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The potentiality of Algorithms and Artificial Intelligence adoption to improve medication management in Primary Care: a Systematic Review

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Abstract

Objectives

The aim of this study is to investigate the effect of artificial Intelligence algorithms on drug management in primary care settings comparing artificial intelligence (AI) or algorithms with standard clinical practice. Secondly, we evaluated what is the most frequently reported type of medication error and the most used AI machine type.

Methods

A systematic review of literature was conducted querying PubMed, Cochrane, and ISI Web of Science, with a narrative synthesis of results. The search strategy and the study selection were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Population, Intervention, Comparator, Outcome (PICO) framework. The methodological quality of included studies was appraised adopting the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies for non-randomized controlled trials (NRCTs) as well as the Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs).

Results

Studies reported in different ways the effective reduction of medication error. Ten out of 14 included studies, corresponding to 71% of articles, reported a reduction in medication errors, supporting the hypothesis that artificial intelligence is an important tool for patient safety.

Conclusion

This study highlights how a safe application of AI in primary care is possible and provides an important tool to support the physician with drug management in non-hospital environments.

Keywords Artificial intelligence; Primary Care; Public Health; Legal Medicine; Risk Management

Strengths and limitations of this study

- To our knowledge this is the first systematic review of literature evaluating the impact of Artificial Intelligence on medications error in a primary care setting.
- Rigorous and reproducible methodology according to the PRISMA guidelines.
- Multidisciplinary approach to the investigated topic.
- Small number of included studies and high heterogeneity across them.
- Difficulties in evaluating the most suitable medication class for AI applications due to missing data.

Introduction

Patient safety was defined by the IOM as “the prevention of harm to patients”(1), focusing the attention on the need to take preventive action to ensure a safe process of care for the patient. Applying this definition into clinical practice, it can be considered as that portion of health care systems that is responsible of minimizing the incidence and impact of adverse events and maximizing recovery from such events (2). Although the IOM Roundtable was careful to distinguish adverse events deriving from medications misuse from error, the adverse events category became a common reference point for conceptualizing patient safety as a component of quality. In this scenario, adverse event and medication errors become comparable as a goal of the patient safety assurance process. An error is defined as the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim (3); thus an adverse event is an injury caused by medical management rather than the underlying condition of the patient. An adverse event attributable to error is a "preventable adverse event"(4). It is therefore essential to deepen the knowledge of what can be considered a medication error. A medication error is any error that occurs at any point in the medication use process. Medication errors and error-related adverse drug events (ADEs) can be thus considered as a common event, responsible for considerable patient harm, leading to morbidity, hospitalisation, increased healthcare costs and, in some cases, death (5). Kohn et al. in 2000 reported that 10% of the total medical errors are related to medication use, with 70% of total registered errors considered preventable (6). It has been estimated by the Institute of Medicine that medication errors cause 1 of 131 outpatient and 1 of 854 inpatient deaths (7) contributing substantially to healthcare costs and representing a public concern in healthcare systems across the world (8). Adverse events could result from people experiencing adverse drug reactions (not usually preventable) or could be due to medication errors (usually preventable) (9). Even though prescribing errors are one of the most common causes of preventable iatrogenic injury, there have been relatively few studies of their incidence and causes.

Moreover, the majority of the studies that have been carried out have been based in secondary care (10). Few studies approach the problem by proposing solutions based on the application of innovative technologies, which can not only reduce the incidence of adverse events but also support the practitioner during the daily clinical activities.

This study partially fills the literature gap in primary care about this topic. Primary care is a patient and community relationship system with a series of professional figures and health and socio-sanitary structures to guarantee the first contact in case of acute diseases and the taking in charge (access and continuity of care) for chronic conditions. In this system, an important role is assumed by the work of multi-professional and multidisciplinary assistance teams and by the engagement of patients, caregivers and communities. Almost 75% of outpatient visits by family doctors and general practitioners involve continuation or initiation of drug therapy (10). Moreover, caregivers of adults aged 65 or over are usually tasked with complicated medication management, including medication organization, administration, and communication with healthcare providers. Finally, patients over 65 are at increased risk of adverse effects due to polypharmacy, making caregiver attention to medication management critical to ensuring patient safety (11). In this context, since primary care is a heterogeneous and complex setting, drug-related errors and adverse events are common due to the enormous amount of drugs used by outpatients in unmonitored situations. The potential risk of an adverse event due to an error in the use or prescription of drugs in the outpatient setting therefore is much higher than in the hospital setting (12).

Technology’s role in healthcare has expanded exponentially over the last 20 years and figures to increase in conjunction with societal technological advancements (13). Applications of omics technologies, the digitalisation of biology and the applications of machine learning and artificial intelligence (AI) are accelerating disease insights at pace with translation of discoveries into new diagnostic tests and treatments (14). AI can be considered a new methodology rather than a support tool. That means the methods behind AI are (mathematical) learning algorithms that adjust the parameters of methods via learning rules (15). The ability to adapt to the needs of the patient make this tool an important means to achieve the goal of a personalized medicine. Personalized medicine (PM) is a novel and topic in the medicine and healthcare sectors. It is a concept that has the potential to transform medical interventions by providing effective, customised therapeutic strategies based on the profile of an individual, while taking into account every patient's personal situation. The power of PM lies not only in treatment, but in prevention, bringing the attention back to preventive intervention to increase patient safety defined above (16). In-home AI systems may potentially improve the quality of life in patients optimizing treatments (17), especially with common, but complex diseases characterized as being ascribed to multiple factors, requiring precise treatments on account of the AI algorithms based on big data. On the other hand, AI-assisted management systems could also help minimize logistics-associated monetary and temporal costs on a larger scale (18). The application of AI tailoring treatment to individual needs leads the way towards the new and enthusiastic concept of “precision health” (19).

Computerized physician order entry and clinical decision support systems are electronic prescribing strategies that are already increasingly used to improve patient safety (20). Despite it might be argued that they usually are immature machines, dependent AI decision support systems, when implemented correctly, already demonstrated to improve

patient safety by allowing error detection, the stratification of patients and drug management (21). While the literature at our disposal is promising in terms of safety outcomes, the evidence in favour of this theory is still not sufficient to ensure a large-scale adoption of these tools and further studies will be needed to ensure a wider number of consents. The aim of this study is to evaluate the effect of algorithms and AI on drug management in a primary care setting. Secondly, we focused on the types of avoided medication errors and the level of autonomy reached by the applied AI machines.

Methods

The synopsis for this systematic review was published in the BMJ Open (23).

Patient and Public Involvement

The involvement of patients or the public in the design, conduct, or reporting of the survey was not suitable for this kind of investigation.

2.1. Literature Search Strategy

A Boolean search string was created using the elements of the PICO model (P, population/patient; I, intervention/indicator; C, comparator/control; and O, outcome) to search for relevant articles in Cochrane Library, Web of Science and PubMed databases (22). References of individual studies were also backchecked. Articles were retrieved from the inception of each database until November 2021. The following search terms were used:

1. Terms related to population: “primary care”, “ambulatory care”, “outpatient care”, “general practitioner”, “general paediatrics”

2. Terms linked to intervention: “artificial intelligence”, “algorithms”, “machine learning”, “deep learning”, “neural networks”

3. Terms related to measured outcomes: “medication error”, “adverse event”, “prescribing error”, “dispensing error”, “administration error”, “monitoring error”, “medication errors reporting”, “medication reconciliation”

This systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for the reporting of systematic reviews (24).

2.2. Inclusion Criteria

The inclusion of relevant studies was based on the following criteria: (1) randomised controlled trials developed in primary care settings; (2) studies comparing the application of AI machines to usual clinical practice; (3) studies applying AI to drug management; (4) studies quantitatively analysing the effectiveness of the intervention in terms of medication error reduction.

We focused on primary studies reporting efficacy results. Only articles written in English and with full texts available and published in peer-reviewed journals were included. After removing duplicate results, four researchers (MS, MTR, SG, GA) independently screened the title and abstract to outline the most appropriate articles. Then, the four researchers performed a full-text screening of each article to determine eligibility.

First, the four researchers screened a pull of 20 articles together, with the aim to fine-tune the screening process and solve eventual misalignments. Secondly, the four researchers independently read the abstracts and proceeded with the selection of the pertinent ones.

During the screening process, the researchers solved any ambiguous situation or bias by discussing together the inclusion or exclusion of the article based on the eligibility criteria identified and their expertise on the topic.

2.3. Data Extraction and Quality Assessment

Data extraction was independently completed by five researchers (GA, MCN, FC, GA, MZ), adopting a standard data-entry electronic form. Data on study characteristics (i.e., author name, country or region of study, year of publication, study design), participants related aspects (i.e., sample size, role, type of specialist, type of patient), intervention-related aspects (i.e., name of the intervention, target and provider of intervention, duration of intervention, type and description of intervention, type of AI, complexity level of the machine, type of medication, type of error), and outcome-related aspects (i.e., outcome measurement tools) were extracted from each included study. The methodological quality of included studies was appraised adopting the Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs) recommended by the National Institute of Health, U.S. Department of Health and Human Services. The tool consists of 14 criteria that are used to assess quality, including whether the study was described as randomized, whether the outcome assessors were blinded, and an assessment of the dropout rate. The criteria were classified as "yes", "no", or "not reported". Quality rates were good, fair, or poor as judged by two independent observers (MCN and GA) following the instructions given by the National Institute of Health and Human Services. If disagreements occurred, the final decision was reached by team consensus. One of the suggested questions, question number 8 "Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?" was not included in the assessment process since not applicable to all the included studies. To achieve a summary score for the proposed questions, a threshold was identified. A potential risk of bias was considered if the answers "no" or "not reported" were selected for the items by the reviewer. The quality of an article was considered "good", if the "yes" answers were ≥75 % of the total; if they were <75 % but ≥ 50 %, an article was scored as "fair"; if they were < 50 %, the article was scored as "poor" (25).

2.4. Data Synthesis

The main features of the articles were extracted and narratively described. The type of applied AI in the included RCTs was described using Hintze classification (26), which allows to differentiate between reactive machines, the most basic type of AI; limited memory, containing machines that can look into the past; theory of mind, with machines able to understand that people, creatures and objects in the world can have thoughts and emotions that affect their own behaviour; finally self-awareness, with machines having consciousness.

The type of avoided error was described using Williams classification (27), defining three categories of medication error, namely prescription errors, the incorrect drug selection for a patient; dispensing errors, including selection of the wrong strength or product, and administration errors, when a discrepancy occurs between the drug received by the patient and the drug therapy intended by the prescriber.

The target populations of the interventions were classified according to Assiri et al. (28) definition of patient at risk of medication errors in community care contexts. In this study, authors reported as risk factors the number of medications used by the patient, increased patient age, comorbidities, use of anticoagulants, cases where more than one physician was involved in patients' care and care being provided by family physicians/general practitioners.

Results

Study selection and characteristics

Out of 1634 articles retrieved from the search string launched in July 2021, seven articles resulted suitable to be included as meeting the inclusion criteria. An update of the same string in September 2021 brought to a total of 716 new articles to be evaluated, 79 of which later resulted to be already found and screened. As result of this second screening, seven new articles were included in the study, reaching a total final number of included articles of 14. The following PRISMA flow diagram reports the systematic review's search and selection process of studies for inclusion (Figure 1) (24). All articles evaluated the risk reduction in medication use achieved by the application of artificial intelligence in primary care. Four out of 14 studies (29–32) were performed in the US, three(33–35) in Canada, one (36) between Canada and the US, two (37,38) in Germany, one (39) in France, one (40) in Spain, one (41) in Ireland, one (42) in England. Articles were published in between 1993 (39) and 2020 (38). Most of the included articles (30,33–35,37–39,41,42) referred to randomised controlled trials conducted in primary care ambulatories (64%) administered by physicians or pharmacists;

four studies (29,32,36,40) (29%) were carried out in primary care clinics, both for long and short stay. Finally, one study was carried out in patients' homes (31) (7%). Six studies (34–38,43) were addressed to physicians (50%), four (31,32,39,42) to patients (29%), three studies (29,33,41) involved both physicians and patients (14%), one study (30) involved pharmacists (30) (7%). Table 1 shows additional characteristics of the included studies.

Table 1. Additional characteristics of the included studies

Author, year country	Name of the intervention	Type of evaluated population	Tpe of patient or health care specialists	Duration of the intervention
Berner ES, 2006, US	The Intervention Rule (Nonsteroidal Anti-inflammatory Drug Gastrointestinal RISK)	at risk	Patients at risk of Gastrointestinal complications	6 months
Fried TR, 2017, US	Tool to Reduce Inappropriate Medications (TRIM)	at risk	Patients aged 65 years and older prescribed ≥ 7 medications	12 months
Muth C,2018, Germany	Prioritising Multimedication in Multimorbidity (PRIMUM)	at risk	Patients aged 60 years and older, with ≥3 chronic conditions, under pharmacological treatment with ≥5 long-term drug prescriptions with systemic effects	9 months
Gurwitz JH, 2008, US and Canada	Computerized provider order entry with clinical decision support system to prevent adverse drug events	at risk	In-patients	12 months
Rieckert A, 2020, Germany	Polypharmacy in chronic diseases: reduction of inappropriate medication and adverse drug events in older populations by electronic decision support (PRIMA-eDS)	at risk	Adults aged 75 years and older using eight or more drugs on a regular basis	24 months
Tamblyn R, 2008, Canada	prescribing alerts generated by computerized drug decision support (CDDS)	not at risk	Patients with at least one prescription by the study physician.	6 months
Tamblyn R,2019, Canada	The medical office of the 21st century (MOXXI)	not at risk	Patients aged 66 years and older	13 months
Bhardwaja B, 2011, US	The Drug Renal Alert Pharmacy (DRAP) Program	at risk	Patients at least 18 years old, with an estimated creatinine clearance of 50 ml/minute or lower, and not receiving dialysis	15 months
Tamblyn R,2012, Canada	MOXXI	not at risk	Patients aged 65 and older who were prescribed psychotropic medication	12 months
Chrischilles, 2014, US	Iowa PHR (personal health record)	not at risk	Adults age 65+	7 months
Clyne B,2015, Ireland	OPTI-SCRIPT study (Optimizing Prescribing for Older People in Primary Care, a cluster-randomized controlled trial)	not at risk	70 yo patients and older	11 months
Holt, TA et al, 2017, England	Effectiveness of a software tool (AURAS-AF [Automated Risk Assessment for Stroke in Atrial Fibrillation]) designed to identify people at risk of stroke, but not receiving treatment, during routine care	at risk	Patients with Atrial fibrillation but not receiving treatment with Oral Anti Coagulants to prevent stroke	6 months

Lopez-Picazo, JJ, 2011, Spain	OMI-ap + PRISMAp	not at risk	All patients in the practice who were older than 14 years of age if they were taking more than 1 drug and therefore at risk for drug interactions	15 months
Matsuyama JR, (1993) France	Medication-event monitoring system (MEMS III)	at risk	Patients with poor to fair metabolic control of diabetes mellitus were enrolled.	11 months

Quality assessment

The quality of included studies was evaluated applying the Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs). Six studies (29,30,35,37–39) were found to be of "good quality", four studies (34,40–42) of "fair quality", and four studies (31–33,36) of "poor quality". Table 2 illustrates the results of the quality assessment process for each included study.

Table 2. Results of quality assessment.

Author(year)	1	2	3	4	5	6	7	9	10	11	12	13	14	Overall
Berner ES, 2006	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	N	Y	Y	G
Bhardwaja B, 2011	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	G
Chrischilles, 2014	Y	N	NR	NR	NR	Y	N	N	NR	Y	N	Y	Y	P
Clyne, B,2015	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	F
Fried TR, 2017	Y	Y	Y	NR	N	Y	N	N	NR	Y	N	Y	NR	P
Gurwitz JH, 2008	Y	Y	Y	NR	NR	Y	Y	N	N	NR	N	NR	NR	P
Holt TA, 2017	Y	Y	Y	NR	Y	Y	NR	Y	NR	Y	Y	Y	Y	F
Lopez-Picazo JJ, 2011	Y	Y	Y	N	Y	Y	NR	NR	NR	Y	N	Y	Y	F
Matsuyama JR, 1993	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	G
Muth C,2018	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	N	Y	Y	G
Rieckert A, 2020	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	G
Tamblyn R, 2008	Y	Y	N	N	NR	Y	Y	N	Y	N	Y	Y	NR	P
Tamblyn R,2012	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	G
Tamblyn R,2019	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	F

Abbreviations: Y, yes; N, no; NR, not reported; G, good quality; F, fair quality, P, poor quality.

Question n 12 "Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?" related to the lowest number of articles respecting the criterion (10), followed by question n 4 "Were study participants and providers blinded to treatment group assignment?", with 8 articles non respecting the blinding process.

Signalling questions:

1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?

2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?

3. Was the treatment allocation concealed (so that assignments could not be predicted)?

4. Were study participants and providers blinded to treatment group assignment?

5. Were the people assessing the outcomes blinded to the participants' group assignments?

6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?

7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?

9. Was there high adherence to the intervention protocols for each treatment group?

10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?

11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?

12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?

13. Were outcomes reported or subgroups analysed prespecified (i.e., identified before analyses were conducted)?

14. Were all randomized participants analysed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?

Outcome categories and measures

The type of avoided error was evaluated adopting William's classification of errors in the use of drugs. Most of the articles (29,32–38,40–42) (79%) evaluated trials avoiding prescribing errors. Two studies (31,39) referred to AI application to avoid administration errors (14%), one study (30) (7%) avoided dispensing errors.

Hintze classification was used to define the level of autonomy reached by AI machines utilized in the trials. Seven out of 14 studies(29,33,36–39,42) described machines that reached level I, seven(30–32,34,35,40,41) out of 14 studies machines that reached level II of autonomy. No studies adopted AI technologies belonging to levels III and IV.

Studies reported in different ways the effective reduction of medication error. Ten out of 14 included studies (29,30,33–36,38,40–42) reported a reduction in medication errors. Four studies (31,32,37,39) didn't report any significant reduction of medication error.

The most frequently applied machine category was "computerised decision support system" (29,30,32–38).

Assiri et al. definition of patient "at risk" was applied to the target populations of the interventions. Fifty-seven percent of interventions (29,30,32,36–39,42) were conducted on subjects at risk of medication error, forty-three percent of studies (31,33–35,40,41) referred to general primary care populations with an average risk of error.

Overprescribing

A total of four studies (33,34,38,41) evaluated the changes that AI application induced in excessive prescribing. One study (38) reported a decrease of prescribed drugs in the intervention group compared with control group (adjusted mean difference −0.45, 95% CI −0.63 to −0.26; $p<0.001$). One study (41) found a reduction in proton pump inhibitor prescribing in the intervention group (adjusted odds ratio = 0.30; 95% CI, 0.14-0.68; $p = .04$). One study (33) described a reduction in therapeutic duplication problems in the intervention group (odds ratio 0.55; p = 0.02), no difference in the overall prevalence of prescribing problems. One study (34)reported a significant 57% (odds ratio: 1.43; $p < 0.0001$) reduction in prevalence of therapeutic duplications in the computer-triggered alert group.

Inappropriate medication

A total of four studies (29,31,32,37) defined risk reduction considering inappropriate medication prescription reduction. One study (29) reported significantly lower mean proportion of cases per physician with unsafe prescriptions for the intervention group compared to the control group after adjustment for baseline rates (F 5 4.24, $p < 0.05$, effect size 5 0.54). One study (31) reported a 18.6% reduction of the use of inappropriate medications in the intervention group,

compared to 27% of control group. One study (37) adopted the Medication Appropriateness Index (MAI sum-score) (27). Results showed that the mean MAI sum scores decreased minimally in both groups 6 months after baseline—by 0.3 points in the intervention group and 0.8 points in the control group—revealing a non-significant adjusted mean difference of 0.7 (95% CI −0.2 to 1.6) points in favour of the control group. One article (32) adopted the Patient Assessment of Care for Chronic Conditions (PACIC) score (28). Results showed that a greater proportion of patients who received the intervention than control patients reported a PACIC score of 11 or 12, but this difference was not significant (29.7% vs 15.6%, p = .06)

Drug interaction

A total of two studies(36,40) esteemed the risk reduction evaluating reported drug interaction before and after the intervention. One study(36) reported that comparing intervention and control units, In a post hoc analysis limited to events that might have been prevented as a result of one or more of the alerts, the rate was 1.55 preventable adverse drug events per 100 resident-months on the intervention units and 1.72 preventable events per 100 resident-months on the control units, for an adjusted rate ratio of 0.89 (95% CI50.61–1.28). One study (40) after the follow-up period, registered 4353 potential clinically relevant interactions (5.3 interactions per 100 patients; 95% CI = 5.2-5.5) for a 21% reduction in comparison to baseline.

Risk of injury

Two studies (35,42) evaluated the risk of adverse events before and after intervention. One study (35) reported a reduction of 1.7 injuries per 1000 patients (95% CI 0.2/1000 to 3.2/ 1000; p = 0.02) after the follow-up phase. The effect of the intervention was greater for patients with higher baseline risks of injury (p < 0.03). One study (42) reported an Incidence of recorded transient ischemic attack higher in the intervention practices (median 10.0 versus 2.3 per 1000 patients with atrial fibrillation; p = 0.027) but, at 12 months, a lower incidence of both all cause stroke (p = 0.06) and haemorrhage (p = 0.054). No adverse effects of the software were reported.

Adherence

One study (39) evaluated the adherence to therapy, finding no statistically significant difference in the nonadherence rates in both groups when comparing pill count data (35%) in the control group with data in the intervention group (60%).

Dosing

One study (30) outlined over the 15-month intervention period a proportion of medication dosing errors in the intervention group significantly lower than the usual care group (33% vs 49%, p < 0.001).

Discussion

This systematic review of literature identified 14 studies respecting all the selected inclusion criteria, all RCTs. To our knowledge, this is the first systematic study evaluating AI application to medication management in a primary care setting. Other recent reviews indagated AI application in patient safety (44) or drug administration in secondary care (45). All employed machines were expected to reduce medication errors by avoiding human mistakes. All authors evaluated medication error reduction through the identification of various parameters, such as emergency room accesses, number of prescribed drugs, adherence to therapy. Within the interventions, the most frequently applied machine category was “computerised decision support system” (29,30,32–38), a software to help clinical-decision making, in which the data of the patient are paired to a computerized clinical knowledge base and patient-specific assessments or recommendations are then presented to the clinician for a decision (46). Out of nine studies applying this machine, seven (29,30,33–36,38) registered a statistically relevant medication errors reduction. This first result might become a starting point for a deeper evaluation of computerised decision support systems to clinical practice on a wider scale in primary care. Only nine articles reported the medication class the experimentation focused on. In four out of fourteen articles (29,35,39,42) the machine was applied to one single class of medications (respectively non-steroidal anti-inflammatory drugs, psychotropic agents, hypoglycaemic agents and oral anticoagulants). All four of the above articles reported a statistically significant reduction of medication error, arguably suggesting the importance to take targeted actions in the process of digital innovation of healthcare. Thus the importance of AI application in the upcoming “precision health” field, a branch of medicine monitoring health and disease based on an individual’s risk (47). The remaining five articles (30–32,36,48) reported the evaluation of AI application on four or more medication classes. The heterogeneity of the application fields and the missing information about medications classes in four out of fourteen

articles didn't allow researchers to achieve the secondary outcome to define what type of drugs might be more suitable for an AI mediated management. Most of trials were carried on by introducing computer devices into physicians' routines. Some of the articles (30,38,39) were able to assess the detected compliance in the intervention groups. In one of the three articles (38), a low level of compliance was registered by investigators, mostly because of the difficulties physicians experienced while interfacing with the software. AlQudah et al. (49) results from a 2021 systematic review found that perceived usefulness and ease of use encourage behavioural intention in healthcare. The results also highlighted the influence expected performance outcomes and effort expectancy have on health workers attitude. Thus, the influence that the idea of an increase in work efficiency, in this case related to the use of technology, might have over the positive attitude of a worker. Priority should therefore be to implement user-friendly solutions in healthcare, allowing their easier adoption. The relationship between social influence and both behavioural intention and usefulness was extensively confirmed. (50) Almost 80% of included trials avoided through the application of AI different types of prescribing errors. Following Williams classification, a prescribing error is the incorrect drug selection for a patient. This definition encompasses all the consequences of wrong dosing, quantity, indication, or prescription of a contraindicated drug. Lack of knowledge of the prescribed drug, its dosage, and of the patient details contribute to prescribing errors. Other contributing factors include illegible handwriting, inaccurate medication anamnesis, confusion with the drug name, inappropriate use of decimal points, use of abbreviations, use of verbal orders (26). It has already been acknowledged that all of the above issues are a frequent due of medical mistakes, since FDA already took actions to fight against this problem (51). De Arajuo et al. (52) in 2019 published a systematic review inquiring causes and solutions. According to the above-mentioned study, a series of policy options were highlighted, including promoting educational classes, implementing digitalised tools, including the patient in the healing process. Ross S et al. in 2013 (53) confirmed this theory, adding workload and overpressure as direct causes of the error development process. Thus, most of solutions relate to education, digitalisation and re-organisation of work, assuming inadequate theoretical preparation, senescent tools and management deficiencies in the caring process. Around 20% of included trials applied AI to processes usually related to administration errors. Williams defined administration errors as those occurring when there is a discrepancy between the drug received by the patient and the drug therapy intended by the prescriber (26). As second most frequent type of error, several studies explored it and tried to come up with a solution. Keers RN et al. study in 2013 (54) focused its attention on nurses role, as the least link of the administration chain. Three main causes of error were identified, namely misinterpretations, knowledge lacks and violations. Two out of the three hypotheses, the educational and management topics, have already been defined in the previous subsection. Hence the need to stress the attention over these topics, especially referring to a primary care setting where caregivers might be in charge of the administration process, as already assessed by different studies, see Yinn et al. (55). Mager et al. (56) in 2007 already highlighted the importance to implement computerized tools to support the administration process. One intervention allowed the avoidance of dispensing errors, which Williams describes as errors occurring at any stage of the dispensing process, from the receipt of the prescription in the pharmacy to the supply of a dispensed medicine to the patient, primarily with drugs that have a similar name (26). Parand A et al. in 2016 (34) suggested as a solution to the increased risk, the inclusion of pharmacists in the process of care, starting from understanding the prescription to storing the medication, pre-monitoring the patient, preparing the medication, giving the medication, (re)storing/discarding the medication and post-monitoring the patient. Among the included studies, Bhardwaja et al. (30) in 2011 reported a significantly reduction of dispensing errors through the application of a computerized tool for pharmacists, strengthening the aforementioned hypothesis (30). Most of the interventions (29,30,32,36–39,42) were conducted on populations considered at risk of medication errors. Although the vastity of primary care scenarios does not allow to refer to a primary care population, the increasing number of elders and the high incidence of chronic diseases in outpatients makes the primary care target group of relevance and worthy of future insights. This account is supported by the effectiveness of interventions observed in the results. Studies already evaluated patients compliance to AI technologies (57), as well as the correlation between compliance and health status of the patient (58). Future studies might investigate whether patients' compliance and risk of medication error could be related. Medication errors are a relevant problem to face also in terms of patient damage and health systems sustainability. (52) As already defined and supported by previous studies, those most frequently related to patients harm occur at the prescribing (56%) and administering (34%) stages of management, respectively representing 56% and 34% of reported errors according to Bates et al. (59). According to Elliot et al.(60), while mostly leading to minor consequences (72%), around 1 in 4 (just under 26%) errors has the potential to cause moderate harm; 2% could potentially result in serious harm. Forensic literature provides many reports of medico-legal consequences of the error in primary care (61). Common consequences faced by physicians after medication errors can include civil actions, criminal charges, and medical board discipline. (7) Although the encouraging results obtained in this study reinforce the idea that AI is a safe and efficient tool, it is important to take into account also the potential arm related to the implementation of AI based interventions. Indeed, Oliva et al.(62) spotted in the failure to protect personal data the main related issue. Also, the lack of transparency of the decisional process of many algorithms (especially if unsupervised) and the reliability of AI devices depends on the quantity and the quality of the training data, not guaranteeing the quality of the machine (62). Thus, it should be a

political priority to reinforce AI regulation and guidelines to prevent the development of AI related errors, with the intention of becoming a support rather than an obstacle to the clinical practitioner. After assessing the problem from both physician and patient point of view, we deemed to be fundamental the definition of its economic impact from the public health system perspective. Worldwide, the cost of medication errors is esteemed to reach 42 billion US dollars per year (52). In 2017, Walsh et al. systematically reviewed a total of 16 economic evaluations on this specific topic. Mean cost per error per study ranged from €2.58 to €111 727.08, suggesting a difficult and not accurate esteem of the global economic burden of this issue (63). At the same time, evaluating AI machines through an economic point of view is particularly difficult due to the missing data on both direct and indirect costs. Among the included articles, Lopez-Picazo et al. in 2011 tried to build a cost-effectiveness model of the analysed intervention(40), esteeming the incremental cost incurred to reduce the mean of potential interactions. The machine was applied to three different interventions, with a mean cost ranging from 4.2 to 32.1 USD per 1% of improvement in 100 patients beyond the control group. Therefore, given the documented large economic impact associated with the cost burden of medication error, policymakers might steer choices focused on the proper allocation of the upcoming funds, related to post COVID-19 recovery plans, to promote a wider adoption of AI machines in the clinical practice. The adoption of a similar instrument by further studies on AI machines might become a fundamental decisional tool. The main strength of this study is its unique value, to our knowledge there is currently no similar systematic review of literature evaluating the impact of Artificial Intelligence on medications error in a primary care setting. In addition, a rigorous methodology was applied to every phase of this article development. Finally, the cooperation with a forensic medicine interns team ensured a coherent error in medicine subject matter allowing further thoughts on the themes of security and applicability of AI. There are several limitations to this systematic review. First of all, the small number of articles at our disposal could not be representative of the total set of different machines currently used in health. The missing attitude in events reporting characterizing primary care might be the main cause of this. Also, the great heterogeneity in results reporting we found in the included articles didn't allow a quantitative synthesis of evidence. Finally, most of the articles didn't report specifications regarding the medication classes involved in the intervention, hence not allowing to define which class was more easily managed through AI application. Further research is needed to evaluate the potential association between patients' compliance and risk of medication error. Additionally, future studies might focus on the application of AI machines on a specific medication class. Moreover, scholars should investigate the accuracy as well as the related sustainability of implementing AI-based digital health solutions in clinical practice.

Conclusions

This study tries to partially fill an important literature gap regarding AI application in primary care. The ambitious aim to systematically approach such an innovative theme brought this review to be particularly difficult to realize and did not allow to end up with a detailed quantitative synthesis. Nevertheless, it was able to strengthen the evidence regarding safeness and accuracy of AI encouraging a wider application of machines even in less controlled environments, such as the ones in which primary care specialists operate.

Figure legend

Figure 1. PRISMA flow diagram of different screening rounds

Conflict of Interests
The authors have no conflict of interest to declare.

Ethical Approval
Formal ethical approval was not required, as primary data were not collected in this study.

Data sharing statement
No additional data available

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Authors' Contributions
The study concept was developed by AO, GD, GDM, MC. The manuscript was drafted by GA, MCN, SG, MZ, GS, FC, GA, MS, MTR and critically revised by AO, GD, GDM, MC. AO, GD, GDM, MC developed and provided feedback for all sections of the review and approved the final manuscript. The search strategy was developed by GA, MCN, SG, MZ, GS, FC, GA, MS, MTR. Study selection was performed by FC, GA, MTR, MZ. Data extraction and quality assessment was performed by GA, MCN, and GA, with GS as a fourth party in case of disagreements. All authors have approved the final version of the manuscript.

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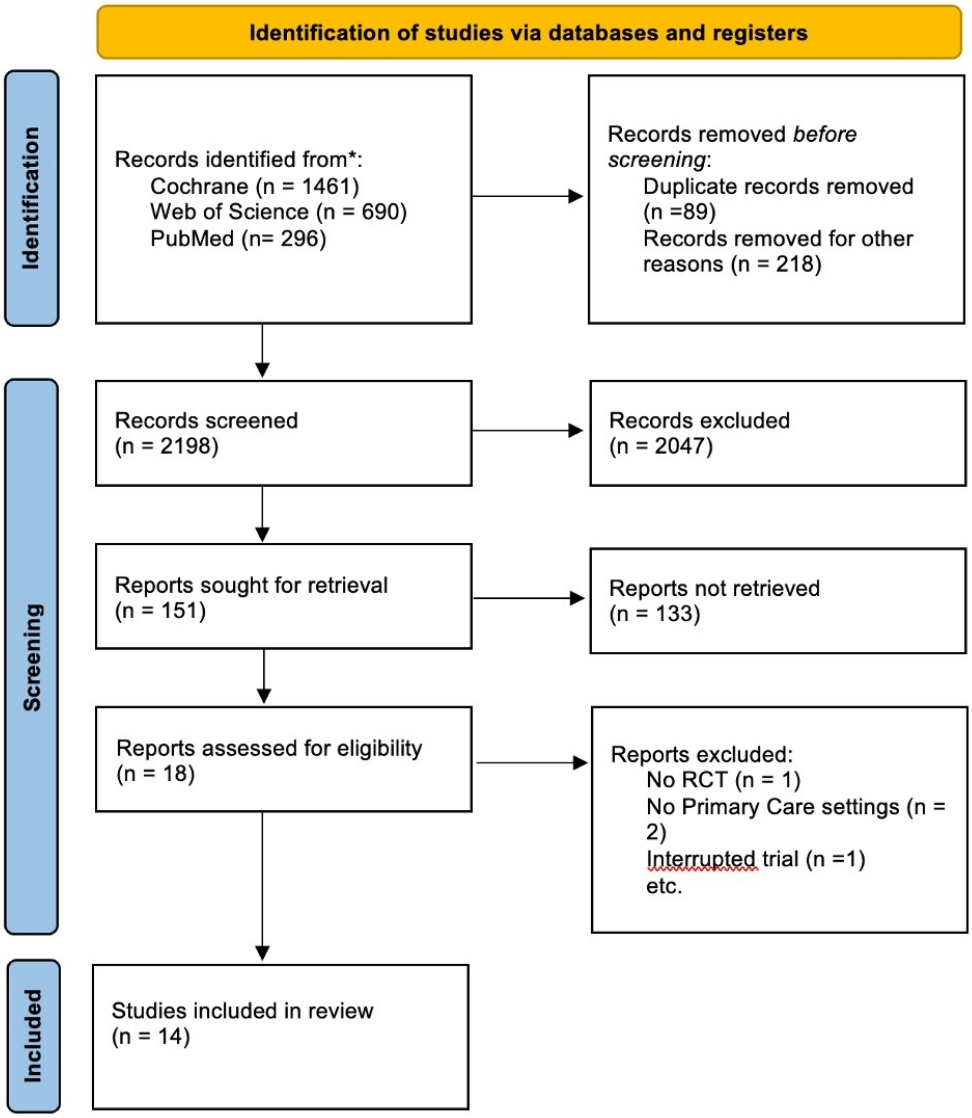

Figure 1. PRISMA flow diagram of different screening rounds

170x193mm (144 x 144 DPI)

PRISMA 2020 Main Checklist

TITLE			
Title	1	Identify the report as a systematic review.	page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	pages 3 and 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	page 5

(continued)

Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	pages 5 and 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	pages 5 and 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	pages 5 and 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	pages 5 and 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	page 6

(continued)

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	not applicable
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	pages 5 and 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	pages 6 and 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	pages 7
Study characteristics	17	Cite each included study and present its characteristics.	pages 6-8

(continued)

Risk of bias in studies	18	Present assessments of risk of bias for each included study.	page 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	not applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	pages 8 and 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	pages 9-11
	23b	Discuss any limitations of the evidence included in the review.	pages 9-11
	23c	Discuss any limitations of the review processes used.	pages 9-11

(continued)

	23d	Discuss implications of the results for practice, policy, and future research.	pages 9-11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	the review was not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	the review protocol is available at 10.1136/bmjopen-2021-057399
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	This study is supported by Fondi di Ateneo, Linea D3.2-Project "Funzioni pubbliche, controllo privato. Profili interdisciplinari sulla governance senza governo della società algoritmica", Università Cattolica del Sacro Cuore, grant number R1024500180. The funder was not involved at all in any phase of the systematic review.
Competing interests	26	Declare any competing interests of review authors.	No competing interests to declare
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	not applicable

PRIMSA Abstract Checklist

TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	No

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The potentiality of Algorithms and Artificial Intelligence adoption to improve medication management in Primary Care: a Systematic Review

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The potentiality of Algorithms and Artificial Intelligence adoption to improve medication management in Primary Care: a Systematic Review

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Abstract

Objectives

The aim of this study is to investigate the effect of artificial Intelligence algorithms on drug management in primary care settings comparing artificial intelligence (AI) or algorithms with standard clinical practice. Secondly, we evaluated what is the most frequently reported type of medication error and the most used AI machine type.

Methods

A systematic review of literature was conducted querying PubMed, Cochrane, and ISI Web of Science until November 2021. The search strategy and the study selection were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Population, Intervention, Comparator, Outcome (PICO) framework. Specifically, the Population chosen was general population of all ages (i.e., including paediatric patients) in primary care settings (i.e., home setting, ambulatory, and nursery homes); the Intervention considered was the analysis AI and/or algorithms (i.e., intelligent programmes or software) application in primary care for reducing medications errors, the Comparator was the general practice and lastly the Outcome was the reduction of preventable medication errors (e.g., overprescribing, inappropriate medication, drug interaction, risk of injury, dosing errors or in an increase of adherence to therapy). The methodological quality of included studies was appraised adopting the Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs).

Results

Studies reported in different ways the effective reduction of medication error. Ten out of 14 included studies, corresponding to 71% of articles, reported a reduction in medication errors, supporting the hypothesis that artificial intelligence is an important tool for patient safety.

Conclusion

This study highlights how a proper application of AI in primary care is possible, since it provides an important tool to support the physician with drug management in non-hospital environments.

Keywords Artificial intelligence; Primary Care; Public Health; Legal Medicine; Risk Management

Strengths and limitations of this study

- To our knowledge this is the first systematic review of literature evaluating the impact of Artificial Intelligence on medications error in a primary care setting.
- Rigorous and reproducible methodology according to the PRISMA guidelines.
- Multidisciplinary approach to the investigated topic.
- Small number of included studies and high heterogeneity across them.
- Difficulties in evaluating the most suitable medication class for AI applications due to missing data.

Introduction

The Institute of Medicine's Roundtable on Evidence-Based Medicine (IOM) defined patient safety as "the prevention of harm to patients"(1), placing attention on the necessity to take precautions to protect a patient's safety during the course of care. Health care systems are accountable for reducing the occurrence and effects of adverse events in clinical practice. (2). The IOM Roundtable was cautious to distinguish between adverse occurrences resulting from pharmaceutical usage and error, but the adverse events category ended up serving as a common starting point for discussions about patient safety as a quality component. In this case, the objective of the patient safety assurance procedure is made to be comparable between adverse events and medication errors. In fact, an adverse event is harm brought on by medical therapy rather than the patient's underlying ailment. Error is defined as the failure to carry out a planned activity as planned or the execution of the incorrect plan to achieve a goal (3). An "adverse incident that could have been prevented" is one that is traceable to error (4). Any mistake that happens during the administration of a medication qualifies as a medication error. Therefore, it is reasonable to assume that medication errors and error-related adverse drug events (ADEs) are frequent occurrences that cause significant patient harm, including morbidity, hospitalization, higher healthcare expenses, and, in some circumstances, death (5). Few research actually address adverse events that occur during primary care; the majority of studies conducted focus mostly on secondary care(6). In order to provide initial contact for acute conditions and care (access and continuity of care) for chronic conditions(7), primary care is a system of relationships between patients and the communities(8) that involves a variety of experts and healthcare services. The continuation or commencement of pharmacological therapy occurs in over 75% of outpatient visits by family doctors and general practitioners, mostly in patients 65 and older(6) . In comparison to the hospital setting, the potential risk of an adverse event resulting from a mistake in medicine use or prescription is much higher in the primary care setting (9). This is because patients over 65 years old frequently have polypharmacy, which is harder to monitor, making caregivers' attention to drug management essential to ensuring patient safety(10). Over the past 20 years, the influence of technology in this setting has increased dramatically(11). By developing new diagnostic procedures and therapies, the use of omics technology, machine learning, and artificial intelligence (AI) is expanding our understanding of disease (12). AI is a new approach that uses learning (mathematical) algorithms that change many parameters. According to the Encyclopedia of Artificial Intelligence, AI is a discipline of science and engineering devoted to the computational understanding and reproducibility of intelligent behaviour(13). This methodology is crucial for achieving the objective of personalized medicine (PM) based on an individual's profile, taking into consideration each patient's unique circumstances since it can be adjusted to the patient's demands. The ability of PM resides in both therapy and prevention targeted at enhancing patient safety(14). Home-based artificial intelligence systems may enhance patients' quality of life through treatment optimization(15), particularly in the case of prevalent but complex diseases. On the other side, AI-assisted management solutions may also reduce the time and money spent on logistics on a bigger scale (16). The innovative idea of "precision health" is made possible by the use of AI to customize treatments to individual needs(17).

Clinical decision support systems and computerized physician order entry are already being utilized more frequently in e-prescribing techniques to increase patient safety(18). AI-dependent decision support systems have previously been proved to increase patient safety by enabling error detection, patient stratification, and drug management at all stages (e.g., prescription, administration and dispensing), despite the fact that it might be argued that they are immature machines(19).

This study aims to assess how AI and algorithms affect medication management in a primary care context. Secondly, is to examine the kinds of therapeutic errors prevented and the degree of autonomy attained by used AI devices.

Methods

The synopsis for this systematic review was published in the BMJ Open(20). This systematic review was reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews(21) and the Synthesis Without Meta-analysis (SWiM) checklist was filled out and is provided as supplementary material.

Patient and Public Involvement

The involvement of patients or the public in the design, conduct, or reporting of the survey was not suitable for this kind of investigation.

2.1. Literature Search Strategy

A Boolean search string was created using the elements of the PICO model (P, population/patient; I, intervention/indicator; C, comparator/control; and O, outcome) to search for relevant articles in Cochrane Library, Web of Science and PubMed databases (22). For the search strategy the following synthetic PICO criteria were addressed:

1. Population: general population of all ages (i.e., including paediatric patients) in primary care settings (i.e., home setting, ambulatory, and nursery homes).

2. Intervention: analysis AI and/or algorithms (i.e., intelligent programmes or software) application in primary care for reducing medications errors.

3. Comparator: general practice.

4. Outcomes: reduction of preventable medication errors (e.g., overprescribing, inappropriate medication, drug interaction, risk of injury, dosing errors or in an increase of adherence to therapy).

References of individual studies were also backchecked. Articles were retrieved from the inception of each database until November 2021. Following, some of the investigated search terms:

1. Terms related to population: “primary care”, “ambulatory care”, “outpatient care”, “general practitioner”, “general paediatrics”.

2. Terms linked to intervention: “artificial intelligence”, “algorithms”, “machine learning”, “deep learning”, “neural networks”.

3. Terms related to measured outcomes: “medication error”, “adverse event”, “prescribing error”, “dispensing error”, “administration error”, “monitoring error”, “medication errors reporting”, “medication reconciliation”.

The full search string is provided in supplementary material 1.

2.2. Inclusion Criteria

The inclusion of relevant studies was based on the following criteria: (1) randomised controlled trials developed in primary care settings; (2) studies comparing the application of AI and/or algorithms to usual clinical practice; (3) studies applying AI and/or algorithms to drug management; (4) studies quantitatively analysing the effectiveness of the intervention in terms of medication error reduction.

In order to be included, articles had to clearly state the application of AI and/or algorithms in the text. A double-check of the intervention methodology was performed to ensure the effective application of AI and/or algorithms, according to the Encyclopedia of Artificial Intelligence definition(23) and the further stated Hintze classification of AI types(24).

We focused on primary studies reporting efficacy results. Only articles written in English and with full texts available and published in peer-reviewed journals were included. After removing duplicate results, four researchers (MS, MTR, SG, GA) independently screened the title and abstract to outline the most appropriate articles. Then, the four researchers performed a full-text screening of each article to determine eligibility.

First, the four researchers screened few of the potentially eligible articles, with the aim to fine-tune the screening process and solve eventual misalignments. Secondly, the four researchers independently read the abstracts and proceeded with the selection of the pertinent ones.
During the screening process, the researchers solved any ambiguous situation or bias by discussing together the inclusion or exclusion of the article based on the eligibility criteria identified and their expertise on the topic. The agreement was handled with tailored group meetings.

2.3. Data Extraction and Quality Assessment

Data extraction was independently completed by five researchers (GA, MCN, FC, GA, MZ), adopting a standard data-entry electronic form. Data on study characteristics (i.e., author name, country or region of study, year of publication, study design), participants related aspects (i.e., sample size, role, type of specialist, type of patient), intervention-related aspects (i.e., name of the intervention, target and provider of intervention, duration of intervention, type and description of intervention, type of AI, complexity level of the machine, type of medication, type of error), and outcome-related aspects (i.e., outcome measurement tools) were extracted from each included study. The electronic data-entry form is available in supplementary material 2. The methodological quality of included studies was appraised adopting the Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs) recommended by the National Institute of Health, U.S. Department of Health and Human Services. The tool consists of 14 criteria that are used to assess quality, including whether the study was described as randomized, whether the outcome assessors were blinded, and an assessment of the dropout rate. The criteria were classified as “yes”, “no”, or “not reported”. Quality rates were good, fair, or poor as judged by two independent observers (MCN and GA) following the instructions given by the National Institute of Health and Human Services. If disagreements occurred, the final decision was reached by team consensus. One of the suggested questions, question number 8 “Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?” was not included in the assessment process since not applicable to all the included studies. To achieve a summary score for the proposed questions, a threshold was identified. A potential risk of bias was considered if the answers “no” or “not reported” were selected for the items by the reviewer. The quality of an article was considered “good”, if the “yes” answers were ≥75 % of the total; if they were <75 % but ≥ 50 %, an article was scored as “fair”; if they were < 50 %, the article was scored as “poor”(25).

2.4. Data Synthesis

The main features of the articles were extracted and narratively described, then displayed in a tabular format. The type of applied AI in the included RCTs was described using Hintze classification(24), which allows to differentiate between reactive machines, the most basic type of AI; limited memory, containing machines that can look into the past; theory of mind, with machines able to understand that people, creatures and objects in the world can have thoughts and emotions that affect their own behaviour; finally self-awareness, with machines having consciousness.
The type of avoided error was described using Williams classification(26), defining three categories of medication error, namely prescription errors, the incorrect drug selection for a patient; dispensing errors, including selection of the wrong strength or product, and administration errors, when a discrepancy occurs between the drug received by the patient and the drug therapy intended by the prescriber.
The target populations of the interventions were classified according to Assiri et al.(27) definition of patient at risk of medication errors in community care contexts. In this study, authors reported as risk factors the number of medications used by the patient, increased patient age, comorbidities, use of anticoagulants, cases where more than one physician was involved in patients’ care and care being provided by family physicians/general practitioners.
A quantitative synthesis was not applied due to heterogeneity issues. The heterogeneity was assessed based on the structural diversity (i.e., different settings, populations targeted, type of intervention, and outcomes) among the studies.

Results

Study selection and characteristics

Out of 1731 articles retrieved from the search string launched in July 2021, seven articles resulted suitable to be included as meeting the inclusion criteria. An update of the same string in November 2021 brought to a total of 716 new articles to be evaluated. A total of 2447 articles was thus retrieved, of which 93 were screened. The total final number of

included articles was 14. The following PRISMA flow diagram reports the systematic review's search and selection process of studies for inclusion (Figure 1)(21). All articles evaluated the risk reduction in medication use achieved by the application of artificial intelligence in primary care. Four out of 14 studies (28–31)(28–31) were performed in the US, three(32–34) in Canada, one (35) between Canada and the US, two (36,37) in Germany, one (38) in France, one (39) in Spain, one (40) in Ireland, one (41) in England. Articles were published in between 1993 (38) and 2020 (37). Most of the included articles (29,32–34,36–38,40,41) referred to randomised controlled trials conducted in primary care ambulatories (64%) administered by physicians or pharmacists; four studies (28,31,35,39) (29%) were carried out in primary care clinics, both for long and short stay. Finally, one study was carried out in patients' homes (30) (7%). Six studies (33–37,42) were addressed to physicians (50%), four (30,31,38,41) to patients (29%), three studies (28,32,40) involved both physicians and patients (14%), one study (29) involved pharmacists (7%). Supplementary material 3 shows additional characteristics of the included studies.

Quality assessment

The quality of included studies was evaluated applying the Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs). Six studies (28,29,34,36–38) were found to be of "good quality", four studies (33,39–41) of "fair quality", and four studies (30–32,35) of "poor quality". Table 1 illustrates the results of the quality assessment process for each included study. Details on quality assessment questionnaire are available in supplementary material 4.

Table 1. Results of quality assessment.

Author(year)	1	2	3	4	5	6	7	9	10	11	12	13	14	Overall
Berner ES, 2006	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	N	Y	Y	G
Bhardwaja B, 2011	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	G
Chrischilles, 2014	Y	N	NR	NR	NR	Y	N	N	NR	Y	N	Y	Y	P
Clyne, B,2015	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	F
Fried TR, 2017	Y	Y	Y	NR	N	Y	N	N	NR	Y	N	Y	NR	P
Gurwitz JH, 2008	Y	Y	Y	NR	NR	Y	Y	N	N	NR	N	NR	NR	P
Holt TA, 2017	Y	Y	Y	NR	Y	Y	NR	Y	NR	Y	Y	Y	Y	F
Lopez-Picazo JJ, 2011	Y	Y	Y	N	Y	Y	NR	NR	NR	Y	N	Y	Y	F
Matsuyama JR, 1993	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	G
Muth C,2018	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	N	Y	Y	G
Rieckert A, 2020	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	G
Tamblyn R, 2008	Y	Y	N	N	NR	Y	Y	N	Y	N	Y	Y	NR	P
Tamblyn R,2012	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	G
Tamblyn R,2019	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	F

Abbreviations: Y, yes; N, no; NR, not reported; G, good quality; F, fair quality, P, poor quality.

Outcome categories and measures

The type of avoided error was evaluated adopting William's classification of errors in the use of drugs. Most of the articles (28,31–37,39–41) (79%) evaluated trials avoiding prescribing errors. Two studies (30,38) referred to AI application to avoid administration errors (14%), one study (29) (7%) avoided dispensing errors.

Hintze classification was used to define the level of autonomy reached by AI machines utilized in the trials. Seven out of 14 studies(28,32,35–38,41) described machines that reached level I, seven(29–31,33,34,39,40) out of 14 studies machines that reached level II of autonomy. No studies adopted AI technologies belonging to levels III and IV.

Studies reported in different ways the effective reduction of medication error. Ten out of 14 included studies (28,29,32–35,37,39–41) reported a reduction in medication errors. Four studies (30,31,36,38) didn't report any significant reduction of medication error.

The most frequently applied machine category was "computerised decision support system" (28,29,31–37).

Assiri et al. definition of patient "at risk" was applied to the target populations of the interventions. Fifty-seven percent of interventions (28,29,31,35–38,41) were conducted on subjects at risk of medication error, forty-three percent of studies (30,32–34,39,40) referred to general primary care populations with an average risk of error.

Overprescribing

A total of four studies (32,33,37,40) evaluated the changes that AI application induced in excessive prescribing. One study (37) reported a decrease of prescribed drugs in the intervention group compared with control group (adjusted mean difference −0.45, 95% CI −0.63 to −0.26; $p<0.001$). One study (40) found a reduction in proton pump inhibitor prescribing in the intervention group (adjusted odds ratio = 0.30; 95% CI, 0.14-0.68; $p = .04$). One study (32) described a reduction in therapeutic duplication problems in the intervention group (odds ratio 0.55; p = 0.02), no difference in the overall prevalence of prescribing problems. One study (33) reported a significant 57% (odds ratio: 1.43; $p < 0.0001$) reduction in prevalence of therapeutic duplications in the computer-triggered alert group.

Inappropriate medication

A total of four studies (28,30,31,36) defined risk reduction considering inappropriate medication prescription reduction. One study (28) reported significantly lower mean proportion of cases per physician with unsafe prescriptions for the intervention group compared to the control group after adjustment for baseline rates (F 5 4.24, $p < 0.05$, effect size 5 0.54). One study (30) reported a 18.6% reduction of the use of inappropriate medications in the intervention group, compared to 27% of control group. One study (36) adopted the Medication Appropriateness Index (MAI sum-score) (27). Results showed that the mean MAI sum scores decreased minimally in both groups 6 months after baseline—by 0.3 points in the intervention group and 0.8 points in the control group—revealing a non-significant adjusted mean difference of 0.7 (95% CI −0.2 to 1.6) points in favour of the control group. One article (31) adopted the Patient Assessment of Care for Chronic Conditions (PACIC) score(43). Results showed that a greater proportion of patients who received the intervention than control patients reported a PACIC score of 11 or 12, but this difference was not significant (29.7% vs 15.6%, $p = .06$)

Drug interaction

A total of two studies (35,39) esteemed the risk reduction evaluating reported drug interaction before and after the intervention. One study(35) reported that comparing intervention and control units, In a post hoc analysis limited to events that might have been prevented as a result of one or more of the alerts, the rate was 1.55 preventable adverse drug events per 100 resident-months on the intervention units and 1.72 preventable events per 100 resident-months on the control units, for an adjusted rate ratio of 0.89 (95% CI50.61–1.28). One study (39) after the follow-up period, registered 4353 potential clinically relevant interactions (5.3 interactions per 100 patients; 95% CI = 5.2-5.5) for a 21% reduction in comparison to baseline.

Risk of injury

Two studies (34,41) evaluated the risk of adverse events before and after intervention. One study (34) reported a reduction of 1.7 injuries per 1000 patients (95% CI 0.2/1000 to 3.2/ 1000; $p = 0.02$) after the follow-up phase. The effect of the intervention was greater for patients with higher baseline risks of injury ($p < 0.03$). One study (41) reported an Incidence of recorded transient ischemic attack higher in the intervention practices (median 10.0 versus 2.3 per 1000 patients with atrial fibrillation; $p = 0.027$) but, at 12 months, a lower incidence of both all cause stroke ($p = 0.06$) and haemorrhage ($p = 0.054$). No adverse effects of the software were reported.

Adherence

One study (38) evaluated the adherence to therapy, finding no statistically significant difference in the nonadherence rates in both groups when comparing pill count data (35%) in the control group with data in the intervention group (60%).

Dosing

One study (29) outlined over the 15-month intervention period a proportion of medication dosing errors in the intervention group significantly lower than the usual care group (33% vs 49%, $p < 0.001$).

Discussion

This systematic review of literature identified 14 papers respecting all inclusion criteria. To our knowledge, this is the first systematic review evaluating AI application to medication management in a primary care setting. In our study, we evaluated whether the use of intelligent algorithms reduced medication errors by avoiding human mistakes. Within the interventions, the most frequently applied machine category was "computerised decision support system" (CDSS) (28,29,31–37), a technological software that uses and analyses patient data (including treatments and outcomes) for clinical decision-making (44). Seven out of nine studies applying this machine (28,29,32–35,37) registered a statistically significant decrease in medication errors. This evidence suggests the need for further larger-scale research on the evaluation of CDSS for clinical practice in primary care. Only nine articles reported the class of drugs the experimentation focused on. In four out of fourteen studies (28,34,38,41) the machine was applied to one single class of medications (respectively non-steroidal anti-inflammatory drugs, psychotropic agents, hypoglycaemic agents and oral anticoagulants). All four of the above articles reported a statistically significant reduction of medication error, arguably suggesting the importance to take targeted actions in the process of digital health innovation with the aim of progressively achieving a "precision health" system (45). The remaining five articles (29–31,35,46) reported the evaluation of AI application on four or more medication classes. The heterogeneity of the application fields and the lack of information on drug classes in four out of fourteen articles did not allow to detect which type of drugs might be most suitable for AI-mediated management. Most of trials were carried on by introducing computer devices into physicians' routines. Some of the articles (29,37,38) were able to assess the detected compliance in the intervention groups. In one of the three articles (37), the investigators reported a low level of compliance, mainly due to the difficulties encountered by physicians in interfacing with the software. AlQudah et al. (47) found that perceived usefulness, ease of use and increased work efficiency -in these cases related to the use of technology- can positively affect employee attitudes. Therefore, user-friendly solutions in the healthcare should be supported (48). In around 80% of the studies, AI prevented prescribing errors. According to Williams' classification, a prescribing error (e.g., wrong indication, dosing) is the incorrect choice of a drug for a patient.(26). The FDA reported that problems associated with prescription are a common cause of medical errors (49). De Arajuo et al. (50) investigated solutions, including the promotion of training courses, the implementation of digitised tools, and the inclusion of the patient in the care process to reduce medical errors. In 2013, Ross et al. (51) reported that excessive workload and overpressure can lead to clinical mistakes. Therefore, as inadequate theoretical preparation, senescent tools and management deficiencies have been identified as sources of clinical errors, most solutions to this problem involve training, digitalisation and re-organisation of work. About 20% of the included studies applied AI to processes usually related to administration errors. Williams defined administration errors as those occurring when there is a discrepancy between the drug received by the patient and the drug therapy intended by the prescriber(26). As the second most frequent type of error, several studies have analysed it and tried to find a solution. Keers et al. (52) focused on nurses role, as the least link of the administration chain. Three main causes of error were identified, namely misinterpretations, knowledge lacks and violations. Two out of the three hypotheses (i.e., the educational and management topics), have already been discussed above. Hence the need to emphasise these issues, especially in a primary care setting where caregivers may be responsible for the administration process (53). Some studies (54) highlighted the importance of implementing computerized tools to support the administration process. One intervention allowed the avoidance of dispensing errors, which Williams describes as errors occurring at any stage of the dispensing process, from the receipt of the prescription in the pharmacy to the supply of a dispensed medicine to the patient, primarily with drugs that have a similar name(26). Parand A et al. in 2016(55) suggested the inclusion of pharmacists in the process of care, from prescription understanding to drug storage, patient pre-monitoring, drug preparation, drug administration, and patient post-monitoring. For example, Bhardwaja et al. (29) reported a significant reduction of dispensing errors through the application of a computerized tool for pharmacists (29). Similar interventions (28,29,31,35–38,41) were conducted on populations at risk of medication errors, e.g. elderly people. Moreover, some studies also evaluated patients compliance to AI technologies (56), as well as the correlation between compliance and health status (57). Future studies might investigate a possible association between patients' compliance and risk of medication error. Medication errors represent a relevant problem in terms of patient damage and health systems sustainability (50). Those most frequently related to patient harm occur in the prescription (56%) and administration (34%) phases, which respectively account for 56% and 34% of reported errors according to Bates et al. (58). Elliot et al.(59) reported that most errors lead to minor consequences (72%), whereas about one in four (just under 26%) have the potential to cause moderate harm and 2% could potentially cause serious harm. The scientific literature provides many reports on medico-legal consequences of the errors in primary care (60), i.e. civil actions, criminal charges, and medical board discipline(61). The evidence of the current study supports the hypothesis that AI is a safe and efficient tool. However, the potential issues associated with AI-based interventions should be considered. Indeed, Oliva et al.(62) identified the lack of personal data protection as the main related issue. Also, the lack of transparency of the decisional process of many algorithms (especially if unsupervised) and the reliability of AI devices

depends on the quantity and the quality of the training data, not guaranteeing the quality of the machine (62). Thus, it should be a political priority to reinforce AI regulation and guidelines to prevent the development of AI-related errors, with the intention of becoming a support rather than an obstacle to the clinical practitioner. After an overall assessment of the issue from physician's and patient's point of view, the economic impact on the public health system should also be evaluated. Worldwide, the cost of medication errors is esteemed to reach 42 billion US dollars per year (50). In 2017, Walsh et al. systematically reviewed a total of 16 economic evaluations on this specific topic. Mean cost per error per study ranged from €2.58 to €111 727.08, suggesting a difficult and not accurate esteem of the global economic burden of this issue (63). At the same time, the economic evaluation of AI machines is particularly difficult due to the lack of data on direct and indirect costs. Among the included articles, in 2011 Lopez-Picazo et al. tried to build a cost-effectiveness model of the analysed intervention (39), esteeming the incremental cost incurred to reduce the mean of potential interactions. The machine was applied to three different interventions, with a mean cost ranging from 4.2 to 32.1 USD per 1% of improvement in 100 patients beyond the control group. Therefore, given the documented large economic impact associated with the cost burden of medication errors, policymakers might steer choices focused on the proper allocation of the upcoming funds, related to post COVID-19 recovery plans, to promote a wider adoption of AI machines in the clinical practice. The adoption of a similar instrument by further studies on AI machines might become a fundamental decisional tool. The main strength of this study is its unique value: to our knowledge, there is currently no similar systematic review of literature evaluating the impact of AI on medications error in a primary care setting. In addition, a rigorous methodology was applied to every phase of this article development. Furthermore, the current topic was analysed from a medico-legal point of view to contextualize the error in healthcare, allowing further reflection on the issues of safety and the applicability of AI. There are several limitations to this systematic review. First of all, the small number of papers could not be representative of all different machines currently used in healthcare. The missing attitude in events reporting characterizing primary care might be the main cause of this. Moreover, the great heterogeneity in results reporting we found in the included articles did not allow a quantitative synthesis of evidence for a meta-analysis. Finally, most of the articles didn't report specifications regarding the medication classes involved in the intervention, hence not allowing to define which class was more easily managed through AI application. Further research is needed to evaluate the potential association between patients' compliance and risk of medication error. Additionally, future studies might focus on the application of AI machines on a specific medication class. Moreover, the accuracy, sustainability and cost-effectiveness of implementing AI-based digital health solutions in clinical practice should be investigated. Further research is also claimed to clarify the technical characteristics of single computer-based interventions for each type of involved technology.

Conclusions

The current study tries to partially fill an important literature gap regarding AI application in primary care. The ambitious aim to systematically approach such an innovative theme brought this review to be particularly difficult to realize and did not allow to end up with a detailed quantitative synthesis. Nevertheless, it was able to strengthen the evidence regarding the aid that AI is able to provide to physicians in managing patients' medication and to encourage a wider application of machines even in less controlled environments, such as the ones in which primary care specialists operate.

Figure legend

Figure 1. PRISMA flow diagram of different screening rounds

Conflict of Interests
The authors have no conflict of interest to declare.

Ethical Approval
Formal ethical approval was not required, as primary data were not collected in this study.

Data sharing statement
No additional data available

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Authors' Contributions
The study concept was developed by AO, GD, GDM, MC. The manuscript was drafted by GA, MCN, SG, MZ, FC, GA, D3.2 group and critically revised by AO, GD, GDM, MC, AHA. AO, GD, GDM, MC developed and provided feedback for all sections of the review and approved the final manuscript. The search strategy was developed by GA, MCN, SG, MZ, FC, GA, D3.2 group. Study selection was performed by FC, GA, MZ, AHA, D3.2 group. Data extraction and quality assessment was performed by GA, MCN, and GA, with SG as a fourth party in case of disagreements. All authors have approved the final version of the manuscript.

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Identification of new studies via databases and registers

Identification

Records identified from:
Databases (n = 2,447)

Records removed before screening:
Duplicate records (n = 307)

Screening

Records screened
(n = 2,140)

Records excluded
(n = 2,047)

Reports sought for retrieval
(n = 93)

Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n = 93)

Reports excluded:
Incorrect study type (n = 15)
Incorrect intervention (n = 57)
Incorrect setting (n = 7)

Included

New studies included in review
(n = 14)

Supplementary Materials

The potentiality of Algorithms and Artificial Intelligence adoption to improve medication management in Primary Care: a Systematic Review

Supplementary materials 1: Full search string.

PubMed

("primary care" OR "ambulatory care" OR "outpatient care" OR "basic health care" OR "basic health-care" OR "basic healthcare" OR "day-to-day health care" OR "first aid" OR "initial medical care" OR " local doctors" OR "local doctor" OR "primary medical care" OR "primary health-care" OR "primary healthcare" OR "general practitioner" OR "general practitioners" OR "GP" OR "GPs" OR "family medicine" OR "general internal medicine" OR "general paediatrics" OR "primary care physician" OR "continuity of care" OR "first aid station" OR "first-aid station" OR "medical station" OR "home care" OR "home assistance" OR "home help")

AND ("artificial intelligence"[MeSH] OR "algorithms" OR "electronic prescribing" OR "Telehealth" OR "machine learning" OR "deep learning" OR "neural networks" OR "Computational Intelligence" OR "Machine Intelligence" OR "Computer Reasoning" OR "telemedicine"[MeSH] OR "m-health" OR "mhealth" OR "mobile health" OR "ehealth" OR "e-health" OR "digital health")

AND ("Medication use" OR "adverse drug events" OR "drug prescription" OR "medication errors"[MeSH] OR "prescription errors" OR "medication error" OR "medication adverse event" OR "drug error" OR "medication administration" OR "medication prescription" OR "medication use" OR "prescribing error" OR "dispensing error" OR "omission error" OR "wrong time error" OR "monitoring error" OR "compliance error")

Web Of Science

("primary care" OR "ambulatory care" OR "outpatient care" OR "basic health care" OR "basic health-care" OR "basic healthcare" OR "day-to-day health care" OR "first aid" OR "initial medical care" OR " local doctors" OR "local doctor" OR "primary medical care" OR "primary health-care" OR "primary healthcare" OR "general practitioner" OR "general practitioners" OR "GP" OR "GPs" OR "family medicine" OR "general internal medicine" OR "general paediatrics" OR "primary care physician" OR "continuity of care" OR "first aid station" OR "first-aid station" OR "medical station" OR "home care" OR "home assistance" OR "home help") AND ("artificial intelligence" OR "algorithms" OR "electronic prescribing" OR "Telehealth" OR "machine learning" OR "deep learning" OR "neural networks" OR "Computational Intelligence" OR "Machine Intelligence" OR "Computer Reasoning" OR "telemedicine" OR "m-health" OR "mhealth" OR "mobile health" OR "ehealth" OR "e-health" OR "digital health") AND ("Medication use" OR "adverse drug events" OR "drug prescription" OR "medication errors" OR "prescription errors" OR "medication error" OR "medication adverse event" OR "drug error" OR "medication administration" OR "medication prescription" OR "medication use" OR "prescribing error" OR "dispensing error" OR "omission error" OR "wrong time error" OR "monitoring error" OR "compliance error")

Cochrane

ID	Search
#1	primary care
#2	ambulatory care
#3	outpatient care
#4	basic health care

#5	basic health-care
#6	basic healthcare
#7	day-to-day health care
#8	first aid
#9	initial medical care
#10	local doctors
#11	local doctor
#12	primary medical care
#13	primary health-care
#14	primary healthcare
#15	general practitioner
#16	general practitioners
#17	GP
#18	GPs
#19	family medicine
#20	general internal medicine
#21	general paediatrics
#22	primary care physician

#23	continuity of care
#24	medical station
#25	home care
#26	home assistance
#27	home help
#28	m-health
#29	mhealth
#30	mobile health
#31	ehealth
#32	e-health
#33	digital health
#34	artificial intelligence
#35	algorithms
#36	electronic prescribing
#37	Telehealth
#38	machine learning
#39	deep learning
#40	neural networks

#41	Machine Intelligence
#42	Computer Reasoning
#43	telemedicine
#44	adverse drug events
#45	drug prescription
#46	medication errors
#47	prescription errors
#48	medication error
#49	medication adverse event
#50	drug error
#51	medication administration
#52	medication prescription
#53	wrong medication use
#54	prescribing error
#55	drug dispensing error
#56	drug omission error
#57	drug monitoring error
#58	drug compliance error

#59	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#60	#28 OR #29 OR #30 OR #31 OR #32 OR #33#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
#61	#44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 #57 OR #58
#62	#59 AND #60 AND #61

Supplementary materials 2: Electronic data-entry form.

DOI	author,year country	Name of intervention	Setting	Population	Sample size	Duration of intervention	Intervention description	Comparator	AI classification	Medication error classification	Severity of avoided reaction	Outcomes	Results	Type of technology	Error description	Study limitations

Supplementary materials 3: Additional characteristics of the included studies

Author, year country	Name of the intervention	Intervention description	Population targeted	Setting	Type of evaluated population	Type of patient or health care specialists	Duration of the intervention
Berner ES, 2006, US	The Intervention Rule (Nonsteroidal Anti-inflammatory Drug Gastrointestinal RISK)	"The Intervention Rule assessed six established risk factors for GI complications from NSAIDs: age, self-assessed health status, diagnosis of rheumatoid arthritis, steroid use, a history of GI hemorrhage or hospitalization for ulcer, and symptoms with NSAIDs.Users enter all six elements into the PDA via pull-down menus and tap a submit button on the PDA screen to receive the score and recommendation."	physicians, patients	primary care residency	at risk	Patients at risk of Gastrointestinal complications	6 months
Fried TR, 2017, US	Tool to Reduce Inappropriate Medications (TRIM)	TRIM (a web tool) extracts data about medications and chronic conditions from the EHR. These data serve as input for automated algorithms identifying medication reconciliation discrepancies, PIMs, and potentially inappropriate regimens.	patients	Primary care clinics	at risk	Patients aged 65 years and older prescribed ≥ 7 medications	12 months
Muth C,2018, Germany	Prioritising Multimedication in Multimorbidity (PRIMUM)	The healthcare assistant conducted a checklist-based interview with patients on medication-related problems and reconciled their medications. Assisted by a computerised decision support system, the general practitioner optimised medication, discussed it with patients and adjusted it accordingly. The control group (CG) continued with usual care.	physicians	General practitioners ambulatories	at risk	Patients aged 60 years and older, with ≥3 chronic conditions, under pharmacological treatment with ≥5 long-term drug prescriptions with systemic effects	9 months
Gurwitz JH, 2008, US and Canada	Computerized provider order entry with clinical decision support system to prevent adverse drug events	For residents on the intervention units, the alerts were displayed in a pop-up box to prescribers in real time when a drug order was entered. The pop-up boxes were informational; they did not require specific actions from the prescriber and did not produce or revise orders automatically	physicians	Long-term care setting	at risk	In-patients	12 months
Rieckert A, 2020, Germany	Polypharmacy in chronic diseases: reduction of inappropriate medication and adverse drug events in older populations by electronic decision support (PRIMA-eDS)	The intervention consisted of a computerised decision support tool providing a comprehensive drug review (see appendix figs 1a and 2a) generated from patient data recorded in the electronic case report form.	Physicians	General practitioners ambulatories	at risk	Adults aged 75 years and older using eight or more drugs on a regular basis	24 months

Tamblyn R, 2008, Canada	prescribing alerts generated by computerized drug decision support (CDDS)	Effectiveness of two approaches to medication alert customization: on-physician-demand versus computer-triggered decision support.	physicians, patients	ambulatory care	not at risk	Patients with at least one prescription by the study physician.	6 months
Tamblyn R,2019, Canada	The medical office of the 21st century (MOXXI)	Physicians in the CDS group obtained information on each patient by downloading updates of dispensed prescriptions from the RAMQ drug-insurance program. These data were integrated into the patient's health record and categorized as having been prescribed by the study physician or by another physician. Alerts were instituted to identify 159 clinically relevant prescribing problems in the elderly, a list established previously by expert consensus:	physicians	Primary care physicians ambulatory	not at risk	Patients aged 66 years and older	13 months
Bhardwaja B, 2011, US	The Drug Renal Alert Pharmacy (DRAP) Program	Patient-specific Clcr data were transferred to the Pharmacy Information Management System (PIMS), enabling PIMS to trigger an alert when a potential medication error was detected—that is, when a target drug was ordered for a patient with a drug-specific Clcr cutoff value. In contrast to alerts that notify the provider at the point of prescription entry, when a potential error was detected in our system, the alert would notify the pharmacist and stop the dispensing process by preventing the prescription label from being printed. In lieu of the prescription label, a medication decision guide was printed for the pharmacist that outlined the process for intervening on the alert. The pharmacist then confirmed if there was an error by using the medication guide, and if needed, contacted the prescribing physician to discuss the potential problem. All pharmacist activities were electronically documented in PIMS.	pharmacists	ambulatory pharmacies	at risk	Patients at least 18 years old, with an estimated creatinine clearance of 50 ml/minute or lower, and not receiving dialysis	15 months
Tamblyn R,2012, Canada	MOXXI	Intervention physicians received information about patient-specific risk of injury computed at the time of each visit using statistical models of nonmodifiable risk factors and psychotropic drug doses. Risk thermometers presented changes in absolute and	physicians	Family physicians ambulatory	not at risk	Patients aged 65 and older who were prescribed psychotropic medication	12 months

		relative risk with each change in drug treatment. Control physicians received commercial drug alerts.					
Chrischilles, 2014, US	Iowa PHR (personal health record)	Iowa PHR is a web-based application that features a tabbed interface design. Users can enter, view, and print their current and past medicines, allergies, health conditions, and health event tracking over time. An embedded tutorial video provides assistance with the system. Iowa PHR displayed a message when a user entered a medication with an associated ACOVE-3 safety concern. The messages were displayed in three levels of increasing detail and complexity to facilitate tiered information take-up: a brief alert containing the basic reason for concern, a summary level that included recommended actions, and a detailed explanation of the alert.	patients	patient's home	not at risk	Adults age 65+	7 months
Clyne B,2015, Ireland	OPTI-SCRIPT study (Optimizing Prescribing for Older People in Primary Care, a cluster-randomized controlled trial)	web-based pharmaceutical treatment algorithms for GPs that provided evidencebased alternative treatment options to PIP drugs, and tailored patient information leaflets	physicians, patients	Ambulatory care	not at risk	70 yo patients and older	11 months
Holt, TA et al, 2017, England	Effectiveness of a software tool (AURAS-AF [Automated Risk Assessment for Stroke in Atrial Fibrillation]) designed to identify people at risk of stroke, but not receiving treatment, during routine care	Screen reminders appeared each time the electronic health records of an eligible patient was accessed until a decision had been taken over OAC treatment	patients	primary care practice	at risk	Patients with Atrial fibrillation but not receiving treatment with Oral Anti Coagulants to prevent stroke	6 months

Lopez-Picazo, JJ, 2011, Spain	OMI-ap + PRISMAp	3 different intervention group: delivery of the interaction report (report group), implementation of clinical educational sessions using the report data (session group), and faceto-face interviews between each family physician and a pharmacist who was specially trained to present the results of the report (face-to-face group)	physicians	Primary care centres	not at risk	All patients in the practice who were older than 14 years of age if they were taking more than 1 drug and therefore at risk for drug interactions	15 months
Matsuyama JR, (1993) France	Medication-event monitoring system (MEMS III)	The microprocessor in the cap records each opening as a presumptive dose, storing the date and time for later retrieval by a microcomputer.	patients	Ambulatory care	at risk	Patients with poor to fair metabolic control of diabetes mellitus were enrolled.	11 months

Supplementary materials 4: Quality assessment questionnaire.

Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs)

Signalling questions:

1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?

2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?

3. Was the treatment allocation concealed (so that assignments could not be predicted)?

4. Were study participants and providers blinded to treatment group assignment?

5. Were the people assessing the outcomes blinded to the participants' group assignments?

6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?

7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?

9. Was there high adherence to the intervention protocols for each treatment group?

10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?

11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?

12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?

13. Were outcomes reported or subgroups analysed prespecified (i.e., identified before analyses were conducted)?

14. Were all randomized participants analysed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?

PRISMA 2020 Main Checklist

TITLE			
Title	1	Identify the report as a systematic review.	page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	pages 3 and 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	page 5

(continued)

Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	pages 5 and 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	pages 5 and 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	pages 5 and 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	pages 5 and 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	page 6

(continued)

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	not applicable
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	pages 5 and 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	pages 6 and 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	pages 7
Study characteristics	17	Cite each included study and present its characteristics.	pages 6-8

(continued)

Risk of bias in studies	18	Present assessments of risk of bias for each included study.	page 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	not applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	pages 8 and 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	pages 9-11
	23b	Discuss any limitations of the evidence included in the review.	pages 9-11
	23c	Discuss any limitations of the review processes used.	pages 9-11

(continued)

	23d	Discuss implications of the results for practice, policy, and future research.	pages 9-11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	the review was not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	the review protocol is available at 10.1136/bmjopen-2021-057399
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	This study is supported by Fondi di Ateneo, Linea D3.2-Project "Funzioni pubbliche, controllo privato. Profili interdisciplinari sulla governance senza governo della società algoritmica", Università Cattolica del Sacro Cuore, grant number R1024500180. The funder was not involved at all in any phase of the systematic review.
Competing interests	26	Declare any competing interests of review authors.	No competing interests to declare
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	not applicable

PRIMSA Abstract Checklist

TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

Synthesis Without Meta-analysis (SWiM) reporting items

The citation for the Synthesis Without Meta-analysis explanation and elaboration article is: Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, Hartmann-Boyce J, Ryan R, Shepperd S, Thomas J, Welch V, Thomson H. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline BMJ 2020;368:l6890 http://dx.doi.org/10.1136/bmj.l6890

SWiM is intended to complement and be used as an extension to PRISMA			
SWiM reporting item	**Item description**	**Page in manuscript where item is reported**	**Other***
Methods			
1 Grouping studies for synthesis	1a) Provide a description of, and rationale for, the groups used in the synthesis (e.g., groupings of populations, interventions, outcomes, study design)	5	
	1b) Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis	5	
2 Describe the standardised metric and transformation methods used	Describe the standardised metric for each outcome. Explain why the metric(s) was chosen, and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted	5	
3 Describe the synthesis methods	Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates	5	
4 Criteria used to prioritise results for summary and synthesis	Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (e.g., based on study design, risk of bias assessments, directness in relation to the review question)	5	

Synthesis Without Meta-analysis (SWiM) reporting items

SWiM reporting item	Item description	Page in manuscript where item is reported	Other*
5 Investigation of heterogeneity in reported effects	State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity	5	
6 Certainty of evidence	Describe the methods used to assess certainty of the synthesis findings	5	
7 Data presentation methods	Describe the graphical and tabular methods used to present the effects (e.g., tables, forest plots, harvest plots). Specify key study characteristics (e.g., study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included	5 5	
Results			
8 Reporting results	For each comparison and outcome, provide a description of the synthesised findings, and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis	6, 10, 11	
Discussion			
9 Limitations of the synthesis	Report the limitations of the synthesis methods used and/or the groupings used in the synthesis, and how these affect the conclusions that can be drawn in relation to the original review question	13	

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
*If the information is not provided in the systematic review, give details of where this information is available (e.g., protocol, other published papers (provide citation details), or website (provide the URL)).

BMJ Open

The potentiality of Algorithms and Artificial Intelligence adoption to improve medication management in Primary Care: a Systematic Review

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Primary Subject Heading:	Public health
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The potentiality of Algorithms and Artificial Intelligence adoption to improve medication management in Primary Care: a Systematic Review

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Abstract

Objectives

The aim of this study is to investigate the effect of artificial Intelligence (AI) and/or algorithms on drug management in primary care settings comparing AI and/or algorithms with standard clinical practice. Secondly, we evaluated what is the most frequently reported type of medication error and the most used AI machine type.

Methods

A systematic review of literature was conducted querying PubMed, Cochrane, and ISI Web of Science until November 2021. The search strategy and the study selection were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Population, Intervention, Comparator, Outcome (PICO) framework. Specifically, the Population chosen was general population of all ages (i.e., including paediatric patients) in primary care settings (i.e., home setting, ambulatory, and nursery homes); the Intervention considered was the analysis AI and/or algorithms (i.e., intelligent programmes or software) application in primary care for reducing medications errors, the Comparator was the general practice and lastly the Outcome was the reduction of preventable medication errors (e.g., overprescribing, inappropriate medication, drug interaction, risk of injury, dosing errors or in an increase of adherence to therapy). The methodological quality of included studies was appraised adopting the Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs).

Results

Studies reported in different ways the effective reduction of medication error. Ten out of 14 included studies, corresponding to 71% of articles, reported a reduction in medication errors, supporting the hypothesis that artificial intelligence is an important tool for patient safety.

Conclusion

This study highlights how a proper application of AI in primary care is possible, since it provides an important tool to support the physician with drug management in non-hospital environments.

Keywords Artificial intelligence; Primary Care; Public Health; Legal Medicine; Risk Management

Strengths and limitations of this study

- To our knowledge this is the first systematic review of literature evaluating the impact of Artificial Intelligence on medications error in a primary care setting.
- Rigorous and reproducible methodology according to the PRISMA guidelines.
- Multidisciplinary approach to the investigated topic.
- Small number of included studies and high heterogeneity across them.
- Difficulties in evaluating the most suitable medication class for AI applications due to missing data.

Introduction

The Institute of Medicine's Roundtable on Evidence-Based Medicine (IOM) defined patient safety as "the prevention of harm to patients"(1), placing attention on the necessity to take precautions to protect a patient's safety during the course of care. Health care systems are accountable for reducing the occurrence and effects of adverse events in clinical practice. (2). The IOM Roundtable was cautious to distinguish between adverse occurrences resulting from pharmaceutical usage and error, but the adverse events category ended up serving as a common starting point for discussions about patient safety as a quality component. In this case, the objective of the patient safety assurance procedure is made to be comparable between adverse events and medication errors. In fact, an adverse event is harm brought on by medical therapy rather than the patient's underlying ailment. Error is defined as the failure to carry out a planned activity as planned or the execution of the incorrect plan to achieve a goal (3). An "adverse incident that could have been prevented" is one that is traceable to error (4). Any mistake that happens during the administration of a medication qualifies as a medication error. Therefore, it is reasonable to assume that medication errors and error-related adverse drug events (ADEs) are frequent occurrences that cause significant patient harm, including morbidity, hospitalization, higher healthcare expenses, and, in some circumstances, death (5). Few research actually address adverse events that occur during primary care; the majority of studies conducted focus mostly on secondary care(6). In order to provide initial contact for acute conditions and care (access and continuity of care) for chronic conditions(7), primary care is a system of relationships between patients and the communities(8) that involves a variety of experts and healthcare services. The continuation or commencement of pharmacological therapy occurs in over 75% of outpatient visits by family doctors and general practitioners, mostly in patients 65 and older(6) . In comparison to the hospital setting, the potential risk of an adverse event resulting from a mistake in medicine use or prescription is much higher in the primary care setting (9). This is because patients over 65 years old frequently have polypharmacy, which is harder to monitor, making caregivers' attention to drug management essential to ensuring patient safety(10). Over the past 20 years, the influence of technology in this setting has increased dramatically(11). By developing new diagnostic procedures and therapies, the use of omics technology, machine learning, and artificial intelligence (AI) is expanding our understanding of disease (12). AI is a growingly applied approach that uses learning (mathematical) algorithms that change many parameters. According to the Encyclopedia of Artificial Intelligence, AI is a discipline of science and engineering devoted to the computational understanding and reproducibility of intelligent behaviour(13). This methodology is crucial for achieving the objective of personalized medicine (PM) based on an individual's profile, taking into consideration each patient's unique circumstances since it can be adjusted to the patient's demands. The ability of PM resides in both therapy and prevention targeted at enhancing patient safety(14). Home-based artificial intelligence systems may enhance patients' quality of life through treatment optimization(15), particularly in the case of prevalent but complex diseases. On the other side, AI-assisted management solutions may also reduce the time and money spent on logistics on a bigger scale (16). The innovative idea of "precision health" is made possible by the use of AI to customize treatments to individual needs(17).

Clinical decision support systems and computerized physician order entry are already being utilized more frequently in e-prescribing techniques to increase patient safety(18). AI-dependent decision support systems have previously been proved to increase patient safety by enabling error detection, patient stratification, and drug management at all stages (e.g., prescription, administration and dispensing), despite the fact that it might be argued that they are immature machines(19). Our initial aim was to focus only on AI-based interventions. Nonetheless, due to the lack of sufficient scientific literature on this specific topic, we decided to expand our investigation to algorithms adopted in drug management as well, starting from the assumption that AI uses algorithms to support clinical practice. This statement does not imply that algorithms and AI might be considered synonyms but highlights our interest in investigating tools that might ease medical workflow in primary care.

Therefore, this study aims to assess how AI and algorithms affect medication management in a primary care context. Secondly, is to examine the kinds of therapeutic errors prevented and the degree of autonomy attained by used AI devices.

Methods

The synopsis for this systematic review was published in the BMJ Open(20). This systematic review was reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews(21) and the Synthesis Without Meta-analysis (SWiM) checklist was filled out and is provided as supplementary material.

Patient and Public Involvement

The involvement of patients or the public in the design, conduct, or reporting of the survey was not suitable for this kind of investigation.

2.1. Literature Search Strategy

A Boolean search string was created using the elements of the PICO model (P, population/patient; I, intervention/indicator; C, comparator/control; and O, outcome) to search for relevant articles in Cochrane Library, Web of Science and PubMed databases (22). For the search strategy the following synthetic PICO criteria were addressed:

1. Population: general population of all ages (i.e., including paediatric patients) in primary care settings (i.e., home setting, ambulatory, and nursery homes).

2. Intervention: analysis AI and/or algorithms (i.e., intelligent programmes or software) application in primary care for reducing medications errors.

3. Comparator: general practice.

4. Outcomes: reduction of preventable medication errors (e.g., overprescribing, inappropriate medication, drug interaction, risk of injury, dosing errors or in an increase of adherence to therapy).

References of individual studies were also backchecked. Articles were retrieved from the inception of each database until November 2021. Following, some of the investigated search terms:

1. Terms related to population: “primary care”, “ambulatory care”, “outpatient care”, “general practitioner”, “general paediatrics”.

2. Terms linked to intervention: “artificial intelligence”, “algorithms”, “machine learning”, “deep learning”, “neural networks”.

3. Terms related to measured outcomes: “medication error”, “adverse event”, “prescribing error”, “dispensing error”, “administration error”, “monitoring error”, “medication errors reporting”, “medication reconciliation”.

The full search string is provided in supplementary material 1.

2.2. Inclusion Criteria

The inclusion of relevant studies was based on the following criteria: (1) randomised controlled trials developed in primary care settings; (2) studies comparing the application of AI and/or algorithms to usual clinical practice; (3) studies applying AI and/or algorithms to drug management; (4) studies quantitatively analysing the effectiveness of the intervention in terms of medication error reduction.

In order to be included, articles had to clearly state the application of AI and/or algorithms in the text. A double-check of the intervention methodology was performed to ensure the effective application of AI and/or algorithms, according to the Encyclopedia of Artificial Intelligence definition(23) and the further stated Hintze classification of AI types(24).

We focused on primary studies reporting efficacy results. Only articles written in English and with full texts available and published in peer-reviewed journals were included. After removing duplicate results, four researchers (MS, MTR, SG, GA) independently screened the title and abstract to outline the most appropriate articles. Then, the four researchers performed a full-text screening of each article to determine eligibility.

First, the four researchers screened few of the potentially eligible articles, with the aim to fine-tune the screening process and solve eventual misalignments. Secondly, the four researchers independently read the abstracts and proceeded with the selection of the pertinent ones.

During the screening process, the researchers solved any ambiguous situation or bias by discussing together the inclusion or exclusion of the article based on the eligibility criteria identified and their expertise on the topic. The agreement was handled with tailored group meetings.

2.3. Data Extraction and Quality Assessment

Data extraction was independently completed by five researchers (GA, MCN, FC, GA, MZ), adopting a standard data-entry electronic form. Data on study characteristics (i.e., author name, country or region of study, year of publication, study design), participants related aspects (i.e., sample size, role, type of specialist, type of patient), intervention-related aspects (i.e., name of the intervention, target and provider of intervention, duration of intervention, type and description of intervention, type of AI, complexity level of the machine, type of medication, type of error), and outcome-related aspects (i.e., outcome measurement tools) were extracted from each included study. The methodological quality of included studies was appraised adopting the Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs) recommended by the National Institute of Health, U.S. Department of Health and Human Services. The tool consists of 14 criteria that are used to assess quality, including whether the study was described as randomized, whether the outcome assessors were blinded, and an assessment of the dropout rate. The criteria were classified as “yes”, “no”, or “not reported”. Quality rates were good, fair, or poor as judged by two independent observers (MCN and GA) following the instructions given by the National Institute of Health and Human Services. If disagreements occurred, the final decision was reached by team consensus. One of the suggested questions, question number 8 “Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?” was not included in the assessment process since not applicable to all the included studies. To achieve a summary score for the proposed questions, a threshold was identified. A potential risk of bias was considered if the answers “no” or “not reported” were selected for the items by the reviewer. The quality of an article was considered “good”, if the “yes” answers were ≥75 % of the total; if they were <75 % but ≥ 50 %, an article was scored as “fair”; if they were < 50 %, the article was scored as “poor”(25).

2.4. Data Synthesis

The main features of the articles were extracted and narratively described, then displayed in a tabular format. The type of applied AI in the included RCTs was described using Hintze classification(24), which allows to differentiate between reactive machines, the most basic type of AI; limited memory, containing machines that can look into the past; theory of mind, with machines able to understand that people, creatures and objects in the world can have thoughts and emotions that affect their own behaviour; finally self-awareness, with machines having consciousness. After an extensive literature search, Hintze classification was chosen based on the following considerations: it offered the most pertinent graduation for our study, it detailed the specifics of the investigated categories, and it was already applied to internationally recognized digital health studies.

The type of avoided error was described using Williams classification(26), defining three categories of medication error, namely prescription errors, the incorrect drug selection for a patient; dispensing errors, including selection of the wrong strength or product, and administration errors, when a discrepancy occurs between the drug received by the patient and the drug therapy intended by the prescriber.

The target populations of the interventions were classified according to Assiri et al.(27) definition of patient at risk of medication errors in community care contexts. In this study, authors reported as risk factors the number of medications used by the patient, increased patient age, comorbidities, use of anticoagulants, cases where more than one physician was involved in patients’ care and care being provided by family physicians/general practitioners.

A quantitative synthesis was not applied due to heterogeneity issues. The heterogeneity was assessed based on the structural diversity (i.e., different settings, populations targeted, type of intervention, and outcomes) among the studies.

Results

Study selection and characteristics

Out of 1731 articles retrieved from the search string launched in July 2021, seven articles resulted suitable to be included as meeting the inclusion criteria. An update of the same string in November 2021 brought to a total of 716 new articles to be evaluated. A total of 2447 articles was thus retrieved, of which 93 were screened. The total final number of included articles was 14. The following PRISMA flow diagram reports the systematic review's search and selection process of studies for inclusion (Figure 1)(21). All articles evaluated the risk reduction in medication use achieved by the application of artificial intelligence in primary care. Four out of 14 studies (28–31)(28–31) were performed in the US, three(32–34) in Canada, one (35) between Canada and the US, two (36,37) in Germany, one (38) in France, one (39) in Spain, one (40) in Ireland, one (41) in England. Articles were published in between 1993 (38) and 2020 (37). Most of the included articles (29,32–34,36–38,40,41) referred to randomised controlled trials conducted in primary care ambulatories (64%) administered by physicians or pharmacists; four studies (28,31,35,39) (29%) were carried out in primary care clinics, both for long and short stay. Finally, one study was carried out in patients' homes (30) (7%). Six studies (33–37,42) were addressed to physicians (50%), four (30,31,38,41) to patients (29%), three studies (28,32,40) involved both physicians and patients (14%), one study (29) involved pharmacists (7%). Supplementary material 2 shows additional characteristics of the included studies.

Quality assessment

The quality of included studies was evaluated applying the Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs). Six studies (28,29,34,36–38) were found to be of "good quality", four studies (33,39–41) of "fair quality", and four studies (30–32,35) of "poor quality". Results of the quality assessment process for each included study and details on the quality assessment questionnaire are available in supplementary material 3.

Outcome categories and measures

The type of avoided error was evaluated adopting William's classification of errors in the use of drugs. Most of the articles (28,31–37,39–41) (79%) evaluated trials avoiding prescribing errors. Two studies (30,38) referred to AI application to avoid administration errors (14%), one study (29) (7%) avoided dispensing errors.

Hintze classification was used to define the level of autonomy reached by AI machines utilized in the trials. Seven out of 14 studies(28,32,35–38,41) described machines that reached level I, seven(29–31,33,34,39,40) out of 14 studies machines that reached level II of autonomy. No studies adopted AI technologies belonging to levels III and IV.

Studies reported in different ways the effective reduction of medication error. Ten out of 14 included studies (28,29,32–35,37,39–41) reported a reduction in medication errors. Four studies (30,31,36,38) didn't report any significant reduction of medication error.

The most frequently applied machine category was "computerised decision support system" (28,29,31–37).

Assiri et al. definition of patient "at risk" was applied to the target populations of the interventions. Fifty-seven percent of interventions (28,29,31,35–38,41) were conducted on subjects at risk of medication error, forty-three percent of studies (30,32–34,39,40) referred to general primary care populations with an average risk of error.

Overprescribing

A total of four studies (32,33,37,40) evaluated the changes that AI application induced in excessive prescribing. One study (37) reported a decrease of prescribed drugs in the intervention group compared with control group (adjusted mean difference −0.45, 95% CI −0.63 to −0.26; p<0.001). One study (40) found a reduction in proton pump inhibitor prescribing in the intervention group (adjusted odds ratio = 0.30; 95% CI, 0.14-0.68; p = .04). One study (32) described a reduction in therapeutic duplication problems in the intervention group (odds ratio 0.55; p = 0.02), no difference in the overall prevalence of prescribing problems. One study (33) reported a significant 57% (odds ratio: 1.43; p < 0.0001) reduction in prevalence of therapeutic duplications in the computer-triggered alert group.

Inappropriate medication

A total of four studies (28,30,31,36) defined risk reduction considering inappropriate medication prescription reduction. One study (28) reported significantly lower mean proportion of cases per physician with unsafe prescriptions for the intervention group compared to the control group after adjustment for baseline rates (F 5 4.24, p < 0.05, effect size 5 0.54). One study (30) reported a 18.6% reduction of the use of inappropriate medications in the intervention group, compared to 27% of control group. One study (36) adopted the Medication Appropriateness Index (MAI sum-score) (27). Results showed that the mean MAI sum scores decreased minimally in both groups 6 months after baseline—by 0.3 points in the intervention group and 0.8 points in the control group—revealing a non-significant adjusted mean difference of 0.7 (95% CI −0.2 to 1.6) points in favour of the control group. One article (31) adopted the Patient Assessment of Care for Chronic Conditions (PACIC) score(43). Results showed that a greater proportion of patients who received the intervention than control patients reported a PACIC score of 11 or 12, but this difference was not significant (29.7% vs 15.6%, p = .06)

Drug interaction

A total of two studies (35,39) esteemed the risk reduction evaluating reported drug interaction before and after the intervention. One study(35) reported that comparing intervention and control units, In a post hoc analysis limited to events that might have been prevented as a result of one or more of the alerts, the rate was 1.55 preventable adverse

drug events per 100 resident-months on the intervention units and 1.72 preventable events per 100 resident-months on the control units, for an adjusted rate ratio of 0.89 (95% CI50.61–1.28). One study (39) after the follow-up period, registered 4353 potential clinically relevant interactions (5.3 interactions per 100 patients; 95% CI = 5.2-5.5) for a 21% reduction in comparison to baseline.

Risk of injury

Two studies (34,41) evaluated the risk of adverse events before and after intervention. One study (34) reported a reduction of 1.7 injuries per 1000 patients (95% CI 0.2/1000 to 3.2/ 1000; $p = 0.02$) after the follow-up phase. The effect of the intervention was greater for patients with higher baseline risks of injury ($p < 0.03$). One study (41) reported an Incidence of recorded transient ischemic attack higher in the intervention practices (median 10.0 versus 2.3 per 1000 patients with atrial fibrillation; $p = 0.027$) but, at 12 months, a lower incidence of both all cause stroke ($p = 0.06$) and haemorrhage ($p = 0.054$). No adverse effects of the software were reported.

Adherence

One study (38) evaluated the adherence to therapy, finding no statistically significant difference in the nonadherence rates in both groups when comparing pill count data (35%) in the control group with data in the intervention group (60%).

Dosing

One study (29) outlined over the 15-month intervention period a proportion of medication dosing errors in the intervention group significantly lower than the usual care group (33% vs 49%, $p < 0.001$).

Discussion

This systematic review of literature identified 14 papers respecting all inclusion criteria. To our knowledge, this is the first systematic review evaluating AI application to medication management in a primary care setting. In our study, we evaluated whether the use of intelligent algorithms reduced medication errors by avoiding human mistakes. Within the interventions, the most frequently applied machine category was “computerised decision support system” (CDSS) (28,29,31–37), a technological software that uses and analyses patient data (including treatments and outcomes) for clinical decision-making (44). Seven out of nine studies applying this machine (28,29,32–35,37) registered a statistically significant decrease in medication errors. This evidence suggests the need for further larger-scale research on the evaluation of CDSS for clinical practice in primary care. Only nine articles reported the class of drugs the experimentation focused on. In four out of fourteen studies (28,34,38,41) the machine was applied to one single class of medications (respectively non-steroidal anti-inflammatory drugs, psychotropic agents, hypoglycaemic agents and oral anticoagulants). All four of the above articles reported a statistically significant reduction of medication error, arguably suggesting the importance to take targeted actions in the process of digital health innovation with the aim of progressively achieving a “precision health” system (45). The remaining five articles (29–31,35,46) reported the evaluation of AI application on four or more medication classes. The heterogeneity of the application fields and the lack of information on drug classes in four out of fourteen articles did not allow to detect which type of drugs might be most suitable for AI-mediated management. Most of trials were carried on by introducing computer devices into physicians’ routines. Some of the articles (29,37,38) were able to assess the detected compliance in the intervention groups. In one of the three articles (37), the investigators reported a low level of compliance, mainly due to the difficulties encountered by physicians in interfacing with the software. AlQudah et al. (47) found that perceived usefulness, ease of use and increased work efficiency -in these cases related to the use of technology- can positively affect employee attitudes. Therefore, user-friendly solutions in the healthcare should be supported (48). In around 80% of the studies, AI prevented prescribing errors. According to Williams' classification, a prescribing error (e.g., wrong indication, dosing) is the incorrect choice of a drug for a patient.(26). The FDA reported that problems associated with prescription are a common cause of medical errors (49). De Arajuo et al. (50) investigated solutions, including the promotion of training courses, the implementation of digitised tools, and the inclusion of the patient in the care process to reduce medical errors. In 2013, Ross et al. (51) reported that excessive workload and overpressure can lead to clinical mistakes. Therefore, as inadequate theoretical preparation, senescent tools and management deficiencies have been identified as sources of clinical errors, most solutions to this problem involve training, digitalisation and re-organisation of work. About 20% of the included studies applied AI to processes usually related to administration errors. Williams defined administration errors as those occurring when there is a discrepancy between the drug received by the patient and the drug therapy intended by the prescriber(26). As the second most frequent type of error, several studies have analysed

it and tried to find a solution. Keers et al. (52) focused on nurses role, as the least link of the administration chain. Three main causes of error were identified, namely misinterpretations, knowledge lacks and violations. Two out of the three hypotheses (i.e., the educational and management topics), have already been discussed above. Hence the need to emphasise these issues, especially in a primary care setting where caregivers may be responsible for the administration process (53). Some studies (54) highlighted the importance of implementing computerized tools to support the administration process. One intervention allowed the avoidance of dispensing errors, which Williams describes as errors occurring at any stage of the dispensing process, from the receipt of the prescription in the pharmacy to the supply of a dispensed medicine to the patient, primarily with drugs that have a similar name(26). Parand A et al. in 2016(55) suggested the inclusion of pharmacists in the process of care, from prescription understanding to drug storage, patient pre-monitoring, drug preparation, drug administration, and patient post-monitoring. For example, Bhardwaja et al. (29) reported a significant reduction of dispensing errors through the application of a computerized tool for pharmacists (29). Similar interventions (28,29,31,35–38,41) were conducted on populations at risk of medication errors, e.g. elderly people. Moreover, some studies also evaluated patients compliance to AI technologies (56), as well as the correlation between compliance and health status (57). Future studies might investigate a possible association between patients' compliance and risk of medication error. Medication errors represent a relevant problem in terms of patient damage and health systems sustainability (50). Those most frequently related to patient harm occur in the prescription (56%) and administration (34%) phases, which respectively account for 56% and 34% of reported errors according to Bates et al. (58). Elliot et al.(59) reported that most errors lead to minor consequences (72%), whereas about one in four (just under 26%) have the potential to cause moderate harm and 2% could potentially cause serious harm. The scientific literature provides many reports on medico-legal consequences of the errors in primary care (60), i.e. civil actions, criminal charges, and medical board discipline(61). The evidence of the current study supports the hypothesis that AI is a safe and efficient tool. However, the potential issues associated with AI-based interventions should be considered. Indeed, Oliva et al.(62) identified the lack of personal data protection as the main related issue. Also, the lack of transparency of the decisional process of many algorithms (especially if unsupervised) and the reliability of AI devices depends on the quantity and the quality of the training data, not guaranteeing the quality of the machine (62). Thus, it should be a political priority to reinforce AI regulation and guidelines to prevent the development of AI-related errors, with the intention of becoming a support rather than an obstacle to the clinical practitioner. After an overall assessment of the issue from physician's and patient's point of view, the economic impact on the public health system should also be evaluated. Worldwide, the cost of medication errors is esteemed to reach 42 billion US dollars per year (50). In 2017, Walsh et al. systematically reviewed a total of 16 economic evaluations on this specific topic. Mean cost per error per study ranged from €2.58 to €111 727.08, suggesting a difficult and not accurate esteem of the global economic burden of this issue (63). At the same time, the economic evaluation of AI machines is particularly difficult due to the lack of data on direct and indirect costs. Among the included articles, in 2011 Lopez-Picazo et al. tried to build a cost-effectiveness model of the analysed intervention (39), esteeming the incremental cost incurred to reduce the mean of potential interactions. The machine was applied to three different interventions, with a mean cost ranging from 4.2 to 32.1 USD per 1% of improvement in 100 patients beyond the control group. Therefore, given the documented large economic impact associated with the cost burden of medication errors, policymakers might steer choices focused on the proper allocation of the upcoming funds, related to post COVID-19 recovery plans, to promote a wider adoption of AI machines in the clinical practice. The adoption of a similar instrument by further studies on AI machines might become a fundamental decisional tool. The main strength of this study is its unique value: to our knowledge, there is currently no similar systematic review of literature evaluating the impact of AI on medications error in a primary care setting. In addition, a rigorous methodology was applied to every phase of this article development. Furthermore, the current topic was analysed from a medico-legal point of view to contextualize the error in healthcare, allowing further reflection on the issues of safety and the applicability of AI. There are several limitations to this systematic review. First of all, the small number of papers could not be representative of all different machines currently used in healthcare. The missing attitude in events reporting characterizing primary care might be the main cause of this. Moreover, the great heterogeneity in results reporting we found in the included articles did not allow a quantitative synthesis of evidence for a meta-analysis. Finally, most of the articles didn't report specifications regarding the medication classes involved in the intervention, hence not allowing to define which class was more easily managed through AI application. Further research is needed to evaluate the potential association between patients' compliance and risk of medication error. Additionally, future studies might focus on the application of AI machines on a specific medication class. Moreover, the accuracy, sustainability and cost-effectiveness of implementing AI-based digital health solutions in clinical practice should be investigated. Further research is also claimed to clarify the technical characteristics of single computer-based interventions for each type of involved technology.

Conclusions

The current study tries to partially fill an important literature gap regarding AI application in primary care. The ambitious aim to systematically approach such an innovative theme brought this review to be particularly difficult to realize and did not allow to end up with a detailed quantitative synthesis. Nevertheless, it was able to strengthen the evidence regarding the aid that AI is able to provide to physicians in managing patients' medication and to encourage a wider application of machines even in less controlled environments, such as the ones in which primary care specialists operate.

Figure legend

Figure 1. PRISMA flow diagram of different screening rounds

Conflict of Interests
The authors have no conflict of interest to declare.

Ethical Approval
Formal ethical approval was not required, as primary data were not collected in this study.

Data sharing statement
No additional data available

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Authors' Contributions
The study concept was developed by AO, GD, GDM, MC. The manuscript was drafted by GA, MCN, SG, MZ, FC, GA, D3.2 group and critically revised by AO, GD, GDM, MC, AHA. AO, GD, GDM, MC developed and provided feedback for all sections of the review and approved the final manuscript. The search strategy was developed by GA, MCN, SG, MZ, FC, GA, D3.2 group. Study selection was performed by FC, GA, MZ, AHA, D3.2 group. Data extraction and quality assessment was performed by GA, MCN, and GA, with SG as a fourth party in case of disagreements. All authors have approved the final version of the manuscript.

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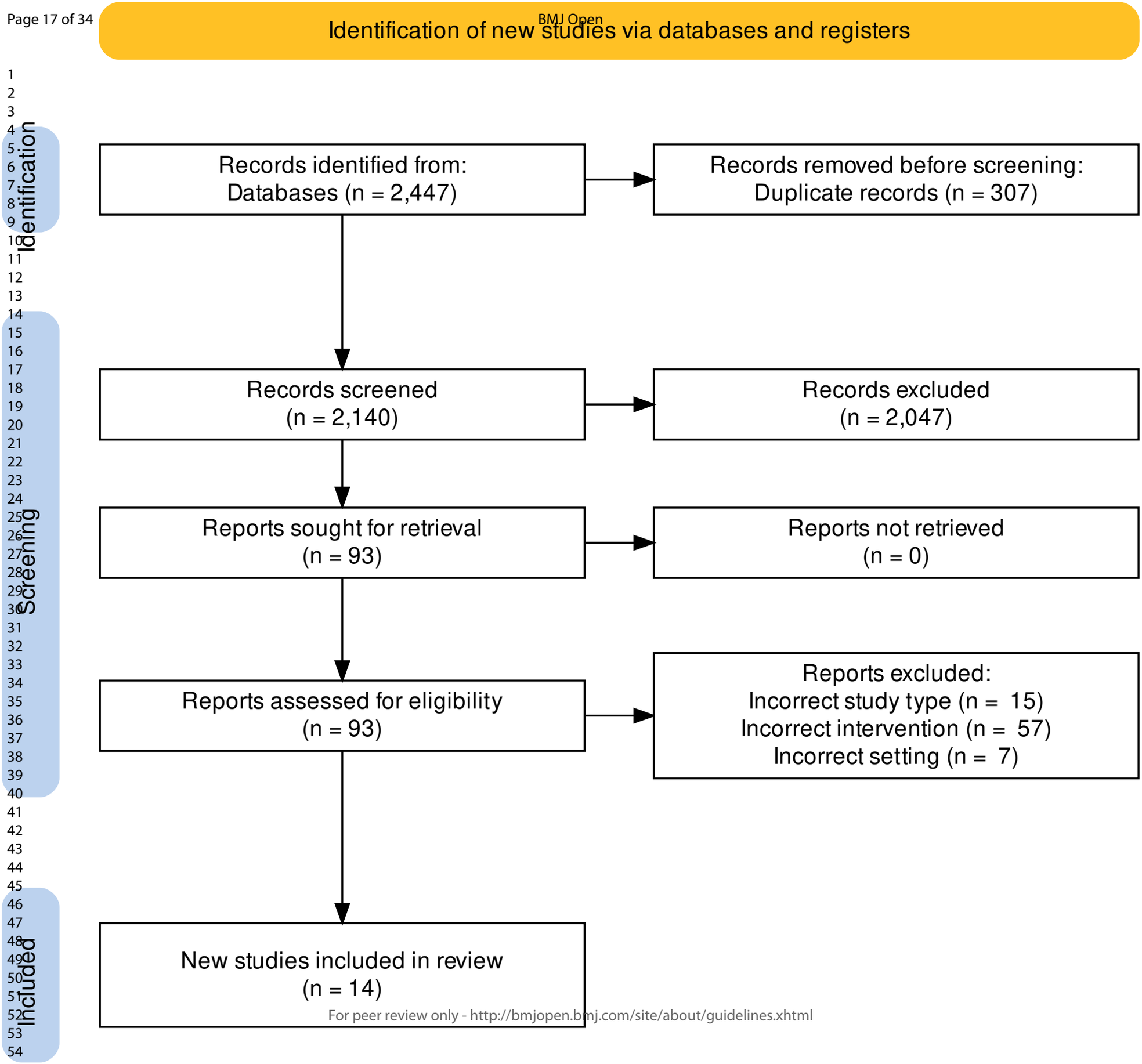

Supplementary Materials

The potentiality of Algorithms and Artificial Intelligence adoption to improve medication management in Primary Care: a Systematic Review

Supplementary materials 1: Full search string.

PubMed

("primary care" OR "ambulatory care" OR "outpatient care" OR "basic health care" OR "basic health-care" OR "basic healthcare" OR "day-to-day health care" OR "first aid" OR "initial medical care" OR " local doctors" OR "local doctor" OR "primary medical care" OR "primary health-care" OR "primary healthcare" OR "general practitioner" OR "general practitioners" OR "GP" OR "GPs" OR "family medicine" OR "general internal medicine" OR "general paediatrics" OR "primary care physician" OR "continuity of care" OR "first aid station" OR "first-aid station" OR "medical station" OR "home care" OR "home assistance" OR "home help")

AND ("artificial intelligence"[MeSH] OR "algorithms" OR "electronic prescribing" OR "Telehealth" OR "machine learning" OR "deep learning" OR "neural networks" OR "Computational Intelligence" OR "Machine Intelligence" OR "Computer Reasoning" OR "telemedicine"[MeSH] OR "m-health" OR "mhealth" OR "mobile health" OR "ehealth" OR "e-health" OR "digital health")

AND ("Medication use" OR "adverse drug events" OR "drug prescription" OR "medication errors"[MeSH] OR "prescription errors" OR "medication error" OR "medication adverse event" OR "drug error" OR "medication administration" OR "medication prescription" OR "medication use" OR "prescribing error" OR "dispensing error" OR "omission error" OR "wrong time error" OR "monitoring error" OR "compliance error")

Web Of Science

("primary care" OR "ambulatory care" OR "outpatient care" OR "basic health care" OR "basic health-care" OR "basic healthcare" OR "day-to-day health care" OR "first aid" OR "initial medical care" OR " local doctors" OR "local doctor" OR "primary medical care" OR "primary health-care" OR "primary healthcare" OR "general practitioner" OR "general practitioners" OR "GP" OR "GPs" OR "family medicine" OR "general internal medicine" OR "general paediatrics" OR "primary care physician" OR "continuity of care" OR "first aid station" OR "first-aid station" OR "medical station" OR "home care" OR "home assistance" OR "home help") AND ("artificial intelligence" OR "algorithms" OR "electronic prescribing" OR "Telehealth" OR "machine learning" OR "deep learning" OR "neural networks" OR "Computational Intelligence" OR "Machine Intelligence" OR "Computer Reasoning" OR "telemedicine" OR "m-health" OR "mhealth" OR "mobile health" OR "ehealth" OR "e-health" OR "digital health") AND ("Medication use" OR "adverse drug events" OR "drug prescription" OR "medication errors" OR "prescription errors" OR "medication error" OR "medication adverse event" OR "drug error" OR "medication administration" OR "medication prescription" OR "medication use" OR "prescribing error" OR "dispensing error" OR "omission error" OR "wrong time error" OR "monitoring error" OR "compliance error")

Cochrane

ID	Search
#1	primary care
#2	ambulatory care
#3	outpatient care
#4	basic health care

#5	basic health-care
#6	basic healthcare
#7	day-to-day health care
#8	first aid
#9	initial medical care
#10	local doctors
#11	local doctor
#12	primary medical care
#13	primary health-care
#14	primary healthcare
#15	general practitioner
#16	general practitioners
#17	GP
#18	GPs
#19	family medicine
#20	general internal medicine
#21	general paediatrics
#22	primary care physician

#23	continuity of care
#24	medical station
#25	home care
#26	home assistance
#27	home help
#28	m-health
#29	mhealth
#30	mobile health
#31	ehealth
#32	e-health
#33	digital health
#34	artificial intelligence
#35	algorithms
#36	electronic prescribing
#37	Telehealth
#38	machine learning
#39	deep learning
#40	neural networks

#41	Machine Intelligence
#42	Computer Reasoning
#43	telemedicine
#44	adverse drug events
#45	drug prescription
#46	medication errors
#47	prescription errors
#48	medication error
#49	medication adverse event
#50	drug error
#51	medication administration
#52	medication prescription
#53	wrong medication use
#54	prescribing error
#55	drug dispensing error
#56	drug omission error
#57	drug monitoring error
#58	drug compliance error

#59 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27

#60 #28 OR #29 OR #30 OR #31 OR #32 OR #33#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43

#61 #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 #57 OR #58

#62 #59 AND #60 AND #61

Supplementary materials 2: Additional characteristics of the included studies

Author, year country	Name of the intervention	Intervention description	Population targeted	Setting	Type of evaluated population	Type of patient or health care specialists	Duration of the intervention
Berner ES, 2006, US	The Intervention Rule (Nonsteroidal Anti-inflammatory Drug Gastrointestinal RISK)	"The Intervention Rule assessed six established risk factors for GI complications from NSAIDs: age, self-assessed health status, diagnosis of rheumatoid arthritis, steroid use, a history of GI hemorrhage or hospitalization for ulcer, and symptoms with NSAIDs.Users enter all six elements into the PDA via pull-down menus and tap a submit button on the PDA screen to receive the score and recommendation."	physicians, patients	primary care residency	at risk	Patients at risk of Gastrointestinal complications	6 months
Fried TR, 2017, US	Tool to Reduce Inappropriate Medications (TRIM)	TRIM (a web tool) extracts data about medications and chronic conditions from the EHR. These data serve as input for automated algorithms identifying medication reconciliation discrepancies, PIMs, and potentially inappropriate regimens.	patients	Primary care clinics	at risk	Patients aged 65 years and older prescribed ≥ 7 medications	12 months
Muth C,2018, Germany	Prioritising Multimedication in Multimorbidity (PRIMUM)	The healthcare assistant conducted a checklist-based interview with patients on medication-related problems and reconciled their medications. Assisted by a computerised decision support system, the general practitioner optimised medication, discussed it with patients and adjusted it accordingly. The control group (CG) continued with usual care.	physicians	General practitioners ambulatories	at risk	Patients aged 60 years and older, with ≥3 chronic conditions, under pharmacological treatment with ≥5 long-term drug prescriptions with systemic effects	9 months
Gurwitz JH, 2008, US and Canada	Computerized provider order entry with clinical decision support system to prevent adverse drug events	For residents on the intervention units, the alerts were displayed in a pop-up box to prescribers in real time when a drug order was entered. The pop-up boxes were informational; they did not require specific actions from the prescriber and did not produce or revise orders automatically	physicians	Long-term care setting	at risk	In-patients	12 months
Rieckert A, 2020, Germany	Polypharmacy in chronic diseases: reduction of inappropriate medication and adverse drug events in older populations by	The intervention consisted of a computerised decision support tool providing a comprehensive drug review (see appendix figs 1a and 2a) generated from patient data recorded in the electronic case report form.	Physicians	General practitioners ambulatories	at risk	Adults aged 75 years and older using eight or more drugs on a regular basis	24 months

	electronic decision support (PRIMA-eDS)						
Tamblyn R, 2008, Canada	prescribing alerts generated by computerized drug decision support (CDDS)	Effectiveness of two approaches to medication alert customization: on-physician-demand versus computer-triggered decision support.	physicians, patients	ambulatory care	not at risk	Patients with at least one prescription by the study physician.	6 months
Tamblyn R,2019, Canada	The medical office of the 21st century (MOXXI)	Physicians in the CDS group obtained information on each patient by downloading updates of dispensed prescriptions from the RAMQ drug-insurance program. These data were integrated into the patient's health record and categorized as having been prescribed by the study physician or by another physician. Alerts were instituted to identify 159 clinically relevant prescribing problems in the elderly, a list established previously by expert consensus:	physicians	Primary care physicians ambulatory	not at risk	Patients aged 66 years and older	13 months
Bhardwaja B, 2011, US	The Drug Renal Alert Pharmacy (DRAP) Program	Patient-specific Clcr data were transferred to the Pharmacy Information Management System (PIMS), enabling PIMS to trigger an alert when a potential medication error was detected—that is, when a target drug was ordered for a patient with a drug-specific Clcr cutoff value. In contrast to alerts that notify the provider at the point of prescription entry, when a potential error was detected in our system, the alert would notify the pharmacist and stop the dispensing process by preventing the prescription label from being printed. In lieu of the prescription label, a medication decision guide was printed for the pharmacist that outlined the process for intervening on the alert. The pharmacist then confirmed if there was an error by using the medication guide, and if needed, contacted the prescribing physician to discuss the potential problem. All pharmacist activities were electronically documented in PIMS.	pharmacists	ambulatory pharmacies	at risk	Patients at least 18 years old, with an estimated creatinine clearance of 50 ml/minute or lower, and not receiving dialysis	15 months

Tamblyn R,2012, Canada	MOXXI	Intervention physicians received information about patient-specific risk of injury computed at the time of each visit using statistical models of nonmodifiable risk factors and psychotropic drug doses. Risk thermometers presented changes in absolute and relative risk with each change in drug treatment. Control physicians received commercial drug alerts.	physicians	Family physicians ambulatory	not at risk	Patients aged 65 and older who were prescribed psychotropic medication	12 months
Chrischilles, 2014, US	Iowa PHR (personal health record)	Iowa PHR is a web-based application that features a tabbed interface design. Users can enter, view, and print their current and past medicines, allergies, health conditions, and health event tracking over time. An embedded tutorial video provides assistance with the system. Iowa PHR displayed a message when a user entered a medication with an associated ACOVE-3 safety concern. The messages were displayed in three levels of increasing detail and complexity to facilitate tiered information take-up: a brief alert containing the basic reason for concern, a summary level that included recommended actions, and a detailed explanation of the alert.	patients	patient's home	not at risk	Adults age 65+	7 months
Clyne B,2015, Ireland	OPTI-SCRIPT study (Optimizing Prescribing for Older People in Primary Care, a cluster-randomized controlled trial)	web-based pharmaceutical treatment algorithms for GPs that provided evidencebased alternative treatment options to PIP drugs, and tailored patient information leaflets	physicians, patients	Ambulatory care	not at risk	70 yo patients and older	11 months
Holt, TA et al, 2017, England	Effectiveness of a software tool (AURAS-AF [Automated Risk Assessment for Stroke in Atrial Fibrillation]) designed to identify people at risk of stroke, but not	Screen reminders appeared each time the electronic health records of an eligible patient was accessed until a decision had been taken over OAC treatment	patients	primary care practice	at risk	Patients with Atrial fibrillation but not receiving treatment with Oral Anti Coagulants to prevent stroke	6 months

	receiving treatment, during routine care						
Lopez-Picazo, JJ, 2011, Spain	OMI-ap + PRISMAp	3 different intervention group: delivery of the interaction report (report group), implementation of clinical educational sessions using the report data (session group), and faceto-face interviews between each family physician and a pharmacist who was specially trained to present the results of the report (face-to-face group)	physicians	Primary care centres	not at risk	All patients in the practice who were older than 14 years of age if they were taking more than 1 drug and therefore at risk for drug interactions	15 months
Matsuyama JR, (1993) France	Medication-event monitoring system (MEMS III)	The microprocessor in the cap records each opening as a presumptive dose, storing the date and time for later retrieval by a microcomputer.	patients	Ambulatory care	at risk	Patients with poor to fair metabolic control of diabetes mellitus were enrolled.	11 months

Supplementary materials 3: Results of quality assessment.

Author(year)	1	2	3	4	5	6	7	9	10	11	12	13	14	Overall
Berner ES, 2006	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	N	Y	Y	G
Bhardwaja B, 2011	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	G
Chrischilles, 2014	Y	N	NR	NR	NR	Y	N	N	NR	Y	N	Y	Y	P
Clyne, B,2015	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	F
Fried TR, 2017	Y	Y	Y	NR	N	Y	N	N	NR	Y	N	Y	NR	P
Gurwitz JH, 2008	Y	Y	Y	NR	NR	Y	Y	N	N	NR	N	NR	NR	P
Holt TA, 2017	Y	Y	Y	NR	Y	Y	NR	Y	NR	Y	Y	Y	Y	F
Lopez-Picazo JJ, 2011	Y	Y	Y	N	Y	Y	NR	NR	NR	Y	N	Y	Y	F
Matsuyama JR, 1993	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	G
Muth C,2018	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	N	Y	Y	G
Rieckert A, 2020	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	G
Tamblyn R, 2008	Y	Y	N	N	NR	Y	Y	N	Y	N	Y	Y	NR	P
Tamblyn R,2012	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	G
Tamblyn R,2019	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	F

Abbreviations: Y, yes; N, no; NR, not reported; G, good quality; F, fair quality, P, poor quality.

Quality Assessment of Controlled Intervention Studies of National Institute of Health for randomized controlled trials (RCTs)

Signalling questions:

1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?

2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?

3. Was the treatment allocation concealed (so that assignments could not be predicted)?

4. Were study participants and providers blinded to treatment group assignment?

5. Were the people assessing the outcomes blinded to the participants' group assignments?

6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?

7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?

9. Was there high adherence to the intervention protocols for each treatment group?

10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?

11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?

12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?

13. Were outcomes reported or subgroups analysed prespecified (i.e., identified before analyses were conducted)?

14. Were all randomized participants analysed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?

PRISMA 2020 Main Checklist

TITLE			
Title	1	Identify the report as a systematic review.	page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	pages 3 and 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	page 5

(continued)

Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	pages 5 and 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	pages 5 and 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	pages 5 and 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	pages 5 and 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	page 6

(continued)

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	not applicable
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	pages 5 and 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	pages 6 and 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	pages 7
Study characteristics	17	Cite each included study and present its characteristics.	pages 6-8

(continued)

Risk of bias in studies	18	Present assessments of risk of bias for each included study.	page 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	not applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	pages 8 and 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	pages 9-11
	23b	Discuss any limitations of the evidence included in the review.	pages 9-11
	23c	Discuss any limitations of the review processes used.	pages 9-11

(continued)

	23d	Discuss implications of the results for practice, policy, and future research.	pages 9-11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	the review was not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	the review protocol is available at 10.1136/bmjopen-2021-057399
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	This study is supported by Fondi di Ateneo, Linea D3.2-Project "Funzioni pubbliche, controllo privato. Profili interdisciplinari sulla governance senza governo della società algoritmica", Università Cattolica del Sacro Cuore, grant number R1024500180. The funder was not involved at all in any phase of the systematic review.
Competing interests	26	Declare any competing interests of review authors.	No competing interests to declare
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	not applicable

PRIMSA Abstract Checklist

TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

Synthesis Without Meta-analysis (SWiM) reporting items

The citation for the Synthesis Without Meta-analysis explanation and elaboration article is: Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, Hartmann-Boyce J, Ryan R, Shepperd S, Thomas J, Welch V, Thomson H. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline BMJ 2020;368:l6890 http://dx.doi.org/10.1136/bmj.l6890

SWiM is intended to complement and be used as an extension to PRISMA			
SWiM reporting item	**Item description**	**Page in manuscript where item is reported**	**Other***
Methods			
1 Grouping studies for synthesis	1a) Provide a description of, and rationale for, the groups used in the synthesis (e.g., groupings of populations, interventions, outcomes, study design)	5	
	1b) Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis	5	
2 Describe the standardised metric and transformation methods used	Describe the standardised metric for each outcome. Explain why the metric(s) was chosen, and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted	5	
3 Describe the synthesis methods	Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates	5	
4 Criteria used to prioritise results for summary and synthesis	Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (e.g., based on study design, risk of bias assessments, directness in relation to the review question)	5	

Synthesis Without Meta-analysis (SWiM) reporting items

SWiM reporting item	Item description	Page in manuscript where item is reported	Other*
5 Investigation of heterogeneity in reported effects	State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity	5	
6 Certainty of evidence	Describe the methods used to assess certainty of the synthesis findings	5	
7 Data presentation methods	Describe the graphical and tabular methods used to present the effects (e.g., tables, forest plots, harvest plots). Specify key study characteristics (e.g., study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included	5 5	
Results			
8 Reporting results	For each comparison and outcome, provide a description of the synthesised findings, and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis	6, 10, 11	
Discussion			
9 Limitations of the synthesis	Report the limitations of the synthesis methods used and/or the groupings used in the synthesis, and how these affect the conclusions that can be drawn in relation to the original review question	13	

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

*If the information is not provided in the systematic review, give details of where this information is available (e.g., protocol, other published papers (provide citation details), or website (provide the URL)).